

Our Ref.: 620-288
RJW/CP6192306

U.S. PATENT APPLICATION

Inventor(s): Alexander W. OXFORD
Richard J. DAVIS
Robert A. COLEMAN
Kenneth L. CLARK
David E. CLARK
Neil V. HARRIS
Garry FENTON
George HYND

Invention: EP₄ RECEPTOR ANTAGONISTS

NIXON & VANDERHYE P.C.
ATTORNEYS AT LAW
1100 NORTH GLEBE ROAD
8TH FLOOR
ARLINGTON, VIRGINIA 22201-4714
(703) 816-4000
Facsimile (703) 816-4100

SPECIFICATION

EP₄ RECEPTOR ANTAGONISTS

This invention relates to EP₄ receptor antagonists, pharmaceutical compositions comprising such compounds, and
5 the use of such compounds and compositions to treat various diseases.

Background to the invention

Prostanoids comprise prostaglandins (PGs) and thromboxanes
10 (Tx_s) and their receptors fall into five different classes (DP, EP, FP, IP and TP) based on their sensitivity to the five naturally occurring prostanoids, PGD₂, PGE₂, PGF_{2α}, PGI₂ and TxA₂, respectively (Coleman, R.A., Prostanoid Receptors. IUPHAR compendium of receptor characterisation and
15 classification, 2nd edition, 338-353, ISBN 0-9533510-3-3, 2000). EP receptors (for which the endogenous ligand is PGE₂) have been subdivided into four types termed EP₁, EP₂, EP₃ and EP₄. These four types of EP receptors have been cloned and are distinct at both a molecular and
20 pharmacological level (Coleman, R.A., 2000)

EP₄ antagonists have been shown to be useful in the treatment of pain, and in particular, in the treatment of primary headache disorders, which include migraines, and
25 secondary headache disorders, such as drug-induced headaches (WO 00/18405 and WO 01/72302). Dilation of the cerebral vasculature and the subsequent stimulation of pain stimulating, perivascular trigeminal sensory afferent nerves is recognised to play an important role in the
30 pathophysiology of migraine. A sterile inflammatory response, associated with activation of cyclooxygenase and the generation of PGE₂, is also implicated in the pathophysiology of migraine. PGE₂ levels have been shown to be raised during migraine attacks and PGE₂ contributes to

the pain of migraine by directly dilating cerebral arteries and by stimulating the release of vasoactive/pro-inflammatory peptides from the trigeminal nerves. These effects of PGE₂ are mediated in whole or in part by EP₄ receptors. Thus, by binding to and preventing the stimulation of EP₄ receptors, EP₄ antagonists may be used to treat the pain of migraine.

EP₄ antagonists may also be useful in treating a number of other conditions and diseases. For example, they may be used in:

the treatment of pain associated with rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis;

the treatment of musculoskeletal pain, lower back and neck pain, sprains and strains, neuropathic pain, sympathetically mediated pain, myositis, pain associated with cancer and fibromyalgia, pain associated with influenza or other viral infections, such as the common cold, rheumatic fever; pain associated with bowel disorders such as non-ulcer dyspepsia, irritable bowel syndrome; non-cardiac chest pain, pain associated with myocardial ischaemia, post-operative pain, headache, toothache and dysmenorrhea. Neuropathic pain syndromes include diabetic neuropathy, sciatica, non-specific lower back pain, multiple sclerosis pain, fibromyalgia, HIV-related neuropathy, post-herpetic neuralgia, trigeminal neuralgia and pain resulting from physical trauma;

the treatment of inflammatory diseases including rheumatoid and osteoarthritis, psoriasis, dermatitis, retinitis, conjunctivitis, asthma, bronchitis, chronic obstructive pulmonary disease, inflammatory bowel disease, colitis, nephritis, gingivitis and hepatitis;

the treatment of cancers including familial adenomatous

polyposis, endometrial carcinoma, colorectal and cervical cancer;

the treatment of bone disorders involving altered bone formation or resorption such as osteoporosis;

5 women's health for the treatment of myometrial and endometrial disorders;

the treatment of gastrointestinal disease including diarrhoea;

10 the treatment of immunological disorders such as autoimmune disease, immunological deficiency diseases, organ transplantation and increasing the latency of HIV infection; the treatment of diseases of abnormal platelet function. (e.g. occlusive vascular diseases);

15 the preparation of a drug with diuretic properties to treat or prevent various oedema, hypertension, premenstrual tension, urinary calculus, oliguria, hyperphosphaturia, mesangial proliferative glomerulonephritis, chronic renal failure or the like;

20 the treatment of impotence or erectile dysfunction, and female sexual dysfunction;

the treatment of hair growth disorders;

the treatment of sleep disorders such as narcolepsy and insomnia;

25 the treatment of cardiovascular diseases and shock states associated with hypotension (e.g. septic shock);

the treatment of neurodegenerative diseases and for preventing neuronal damage following stroke, cardiac arrest, cardiopulmonary bypass, traumatic brain injury or spinal cord injury;

30 the treatment of tinnitus;

the treatment of dependence; and

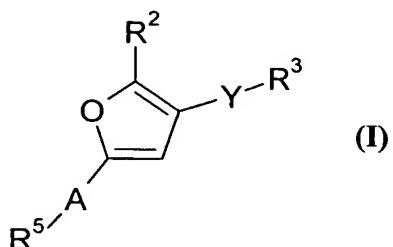
the treatment of complications of diabetes.

Although EP₄ antagonists are known, it is desired to find

novel EP₄ antagonists, and in particular, EP₄ antagonists which are selective against other EP receptors, i.e. EP₁, EP₂ and EP₃.

5 *Summary of the invention*

A first aspect of the present invention provides a compound of formula (I):



or a pharmaceutically acceptable salt thereof for use in a method of therapy, wherein:

R² is H or an optionally substituted C₁₋₄ alkyl group;

Y is either -(CH₂)_n-X-, where n is 1 or 2 and X is O, S, S(=O), S(=O)₂, or NR^{N1}, where R^{N1} is selected from H or optionally substituted C₁₋₄ alkyl, or Y is -C(=O)NR^{N2}-,

where R^{N2} is selected from H, and optionally substituted C₁₋₇ alkyl or C₅₋₂₀ aryl;

R³ is an optionally substituted C₆ aryl group linked to a further optionally substituted C₆ aryl group, wherein if both C₆ aryl groups are benzene rings, there may be an

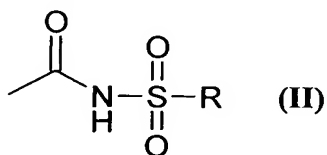
oxygen bridge between the two rings, bound adjacent the link on both rings;

A is a single bond or a C₁₋₃ alkylene group; and

R⁵ is either:

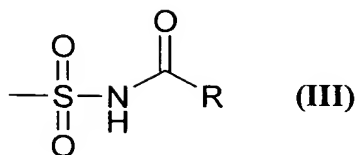
(i) carboxy;

(ii) a group of formula (II):



; or

(iii) a group of formula (III):

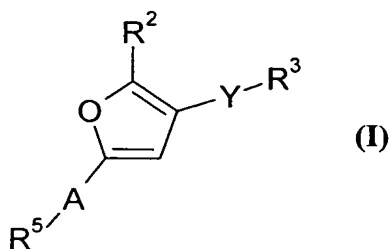


wherein R is optionally substituted C₁₋₇ alkyl, C₅₋₂₀ aryl or NR^{N3}R^{N4}, where R^{N3} and R^{N4} are independently selected from

5 optionally substituted C₁₋₄ alkyl;

(iv) tetrazol-5-yl.

A second aspect of the present invention provides a compound of formula (I):



10

or a salt, solvate and chemically protected form thereof, wherein:

R² is H or an optionally substituted C₁₋₄ alkyl group;

Y is either -(CH₂)_n-X-, where n is 1 or 2 and X is O, S, S(=O), S(=O)₂ or NR^{N1}, where R^{N1} is selected from H or

15 optionally substituted C₁₋₄ alkyl, or Y is -C(=O)NR^{N2}-, where R^{N2} is selected from H, and optionally substituted C₁₋₇ alkyl or C₅₋₂₀ aryl;

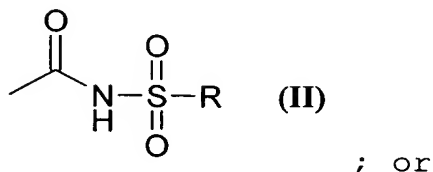
R³ is an optionally substituted C₆ aryl group linked to a further optionally substituted C₆ aryl group, wherein if both C₆ aryl groups are benzene rings, there may be an oxygen bridge between the two rings, bound adjacent the link on both rings;

A is a single bond or a C₁₋₃ alkylene group; and

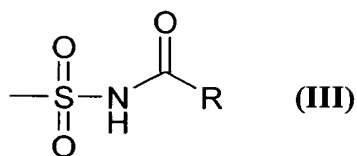
25 R⁵ is either:

(i) carboxy;

(ii) a group of formula (II):



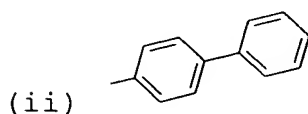
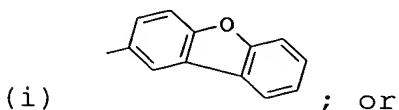
(iii) a group of formula (III):



wherein R is optionally substituted C₁₋₇ alkyl, C₅₋₂₀ aryl or NR^{N3}R^{N4}, where R^{N3} and R^{N4} are independently selected from optionally substituted C₁₋₄ alkyl;

(iv) tetrazol-5-yl,

except that when R² is methyl, Y is -CH₂-O- and R⁵ is carboxy or C₁₋₇ alkyl ester thereof, then R³ is not:



A third aspect of the present invention provides a pharmaceutical composition comprising a compound of formula (I) as defined in the first aspect or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

A further aspect of the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a condition alleviated by antagonism of

an EP₄ receptor.

Another aspect of the present invention provides a method of treating a condition which can be alleviated by antagonism
5 of an EP₄ receptor, which method comprises administering to a patient in need of treatment an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

10 Conditions which can be alleviated by antagonism of an EP₄ receptor are discussed above, and particularly include primary headache disorders, most particularly migraines.

The present invention also provides methods of antagonizing
15 EP₄ receptors, *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound of formula (I).

In some embodiments, the compounds described above may be selective as against antagonism of the other three EP
20 receptors, i.e. EP₁, EP₂ and EP₃. This selectivity allows for targeting of the effect of the compounds of the invention, with possible benefits in the treatment of certain conditions.

25 *Definitions*

Monodentate groups

(i.e groups with one point of covalent attachment)

Alkyl: The term "alkyl" as used herein, pertains to a
30 monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 7 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, and which may be saturated or unsaturated. Thus, the term "alkyl" includes the sub-classes

alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, etc., discussed below.

5 In the context of alkyl groups, the prefixes (e.g. C₁₋₄, C₁₋₇) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term "C₁₋₄ alkyl" as used herein, pertains to an alkyl group having from 1 to 4 carbon atoms. Examples of groups of alkyl groups include C₁₋₄ alkyl ("lower alkyl") and C₁₋₇ alkyl. Note that the first prefix
10 may vary according to other limitations; for example, for unsaturated alkyl groups, the first prefix must be at least 2; for cyclic alkyl groups, the first prefix must be at least 3; etc.

15 Examples of saturated alkyl groups include, but are not limited to, methyl (C₁), ethyl (C₂), propyl (C₃), butyl (C₄), pentyl (C₅), hexyl (C₆) and heptyl (C₇).

20 Examples of saturated linear alkyl groups include, but are not limited to, methyl (C₁), ethyl (C₂), n-propyl (C₃), n-butyl (C₄), n-pentyl (amyl) (C₅), n-hexyl (C₆), and n-heptyl (C₇).

25 Examples of saturated branched alkyl groups include iso-propyl (C₃), iso-butyl (C₄), sec-butyl (C₄), tert-butyl (C₄), iso-pentyl (C₅), and neo-pentyl (C₅).

Alkenyl: The term "alkenyl" as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds.
30 Examples of groups of alkenyl groups include C₂₋₄ alkenyl and C₂₋₇ alkenyl. Examples of alkenyl groups include, but are not limited to, ethenyl (vinyl, -CH=CH₂), 1-propenyl (-CH=CH-CH₃), 2-propenyl (allyl, -CH-CH=CH₂), isopropenyl (1-methylvinyl, -C(CH₃)=CH₂), butenyl (C₄), pentenyl (C₅), and

hexenyl (C_6).

Alkynyl: The term "alkynyl" as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds.

5 Examples of groups of alkynyl groups include C_{2-4} alkynyl and C_{2-7} alkynyl. Examples of alkynyl groups include, but are not limited to, ethynyl (ethinyl, $-C\equiv CH$) and 2-propynyl (propargyl, $-CH_2-C\equiv CH$).

10 Cycloalkyl: The term "cycloalkyl" as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a carbocyclic ring of a carbocyclic compound, which carbocyclic ring may be
15 saturated or unsaturated, which moiety has from 3 to 7 carbon atoms (unless otherwise specified), including from 3 to 7 ring atoms. Thus, the term "cycloalkyl" includes the sub-classes cycloalkenyl and cycloalkynyl. Preferably, each ring has from 3 to 7 ring atoms. Examples of groups of
20 cycloalkyl groups include C_{3-7} cycloalkyl.

Examples of cycloalkyl groups include, but are not limited to, those derived from:

saturated monocyclic hydrocarbon compounds:

25 cyclopropane (C_3), cyclobutane (C_4), cyclopentane (C_5), cyclohexane (C_6), cycloheptane (C_7), methylcyclopropane (C_4), dimethylcyclopropane (C_5), methylcyclobutane (C_5), dimethylcyclobutane (C_6), methylcyclopentane (C_6), dimethylcyclopentane (C_7), methylcyclohexane (C_7);

30 unsaturated monocyclic hydrocarbon compounds:

cyclopropene (C_3), cyclobutene (C_4), cyclopentene (C_5), cyclohexene (C_6), methylcyclopropene (C_4), dimethylcyclopropene (C_5), methylcyclobutene (C_5), dimethylcyclobutene (C_6), methylcyclopentene (C_6),

dimethylcyclopentene (C₇), methylcyclohexene (C₇);

Heterocyclyl: The term "heterocyclyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified), of which from 1 to 10 are ring heteroatoms. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms.

10

In this context, the prefixes (e.g. C₃₋₂₀, C₃₋₇, C₅₋₆, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C₅₋₆ heterocyclyl" as used herein, pertains to a heterocyclyl group having 5 or 6 ring atoms. Examples of groups of heterocyclyl groups include C₃₋₂₀ heterocyclyl, C₅₋₂₀ heterocyclyl, C₃₋₁₅ heterocyclyl, C₅₋₁₅ heterocyclyl, C₃₋₁₂ heterocyclyl, C₅₋₁₂ heterocyclyl, C₃₋₁₀ heterocyclyl, C₅₋₁₀ heterocyclyl, C₃₋₇ heterocyclyl, C₅₋₇ heterocyclyl, and C₅₋₆ heterocyclyl.

20

Examples of monocyclic heterocyclyl groups include, but are not limited to, those derived from:

N₁: aziridine (C₃), azetidine (C₄), pyrrolidine

25 (tetrahydropyrrole) (C₅), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C₅), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C₅), piperidine (C₆),

dihydropyridine (C₆), tetrahydropyridine (C₆), azepine (C₇);

O₁: oxirane (C₃), oxetane (C₄), oxolane (tetrahydrofuran) (C₅), oxole (dihydrofuran) (C₅), oxane (tetrahydropyran) (C₆), dihydropyran (C₆), pyran (C₆), oxepin (C₇);

30

S₁: thiirane (C₃), thietane (C₄), thiolane (tetrahydrothiophene) (C₅), thiane (tetrahydrothiopyran) (C₆), thiepane (C₇);

O₂: dioxolane (C₅), dioxane (C₆), and dioxepane (C₇);

O₃: trioxane (C₆);

N₂: imidazolidine (C₅), pyrazolidine (diazolidine) (C₅),
imidazoline (C₅), pyrazoline (dihydropyrazole) (C₅),

5 piperazine (C₆);

N₁O₁: tetrahydrooxazole (C₅), dihydrooxazole (C₅),
tetrahydroisoxazole (C₅), dihydroisoxazole (C₅), morpholine
(C₆), tetrahydrooxazine (C₆), dihydrooxazine (C₆), oxazine
(C₆);

10 N₁S₁: thiazoline (C₅), thiazolidine (C₅),
thiomorpholine (C₆);

N₂O₁: oxadiazine (C₆);

O₁S₁: oxathiole (C₅) and oxathiane (thioxane) (C₆); and,

N₁O₁S₁: oxathiazine (C₆).

15

Aryl: The term "aryl" as used herein, pertains to a
monovalent moiety obtained by removing a hydrogen atom from
an aromatic ring atom of an aromatic compound, which moiety
has from 3 to 20 ring atoms (unless otherwise specified).

20 Preferably, each ring has from 5 to 7 ring atoms.

In this context, the prefixes (e.g. C₃₋₂₀, C₅₋₇, C₅₋₆, etc.)
denote the number of ring atoms, or range of number of ring
atoms, whether carbon atoms or heteroatoms. For example,

25 the term "C₅₋₆ aryl" as used herein, pertains to an aryl
group having 5 or 6 ring atoms. Examples of groups of aryl
groups include C₃₋₂₀ aryl, C₅₋₂₀ aryl, C₅₋₁₅ aryl, C₅₋₁₂ aryl, C₅₋₁₀
aryl, C₅₋₇ aryl, C₅₋₆ aryl, C₅ aryl, and C₆ aryl.

30 The ring atoms may be all carbon atoms, as in "carboaryl
groups". Examples of carboaryl groups include C₃₋₂₀
carboaryl, C₅₋₂₀ carboaryl, C₅₋₁₅ carboaryl, C₅₋₁₂ carboaryl,
C₅₋₁₀ carboaryl, C₅₋₇ carboaryl, C₅₋₆ carboaryl, C₅ carboaryl,
and C₆ carboaryl.

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e. phenyl) (C₆), naphthalene (C₁₀), azulene (C₁₀), anthracene (C₁₄),
5 phenanthrene (C₁₄), naphthacene (C₁₈), and pyrene (C₁₆).

Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indane (e.g., 2,3-dihydro-
10 1H-indene) (C₉), indene (C₉), isoindene (C₉), tetraline (1,2,3,4-tetrahydronaphthalene (C₁₀), acenaphthene (C₁₂), fluorene (C₁₃), phenalene (C₁₃), acephenanthrene (C₁₅), and aceanthrene (C₁₆).

15 Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroaryl groups". Examples of heteroaryl groups include C₃₋₂₀ heteroaryl, C₅₋₂₀ heteroaryl, C₅₋₁₅ heteroaryl, C₅₋₁₂ heteroaryl, C₅₋₁₀ heteroaryl, C₅₋₇ heteroaryl, C₅₋₆ heteroaryl, C₅ heteroaryl, and C₆ heteroaryl.

20

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

N₁: pyrrole (azole) (C₅), pyridine (azine) (C₆);

O₁: furan (oxole) (C₅);

25 S₁: thiophene (thiole) (C₅);

N₁O₁: oxazole (C₅), isoxazole (C₅), isoxazine (C₆);

N₂O₁: oxadiazole (furazan) (C₅);

N₃O₁: oxatriazole (C₅);

N₁S₁: thiazole (C₅), isothiazole (C₅);

30 N₂: imidazole (1,3-diazole) (C₅), pyrazole

(1,2-diazole) (C₅), pyridazine (1,2-diazine) (C₆),

pyrimidine (1,3-diazine) (C₆), pyrazine (1,4-diazine) (C₆);

N₃: triazole (C₅), triazine (C₆); and,

N₄: tetrazole (C₅).

Examples of heteroaryl groups which comprise fused rings, include, but are not limited to:

C₉ (with 2 fused rings) derived from benzofuran (O₁),
5 isobenzofuran (O₁), indole (N₁), isoindole (N₁), indolizine (N₁), indoline (N₁), isoindoline (N₁), purine (N₄) (e.g., adenine, guanine), benzimidazole (N₂), indazole (N₂), benzoxazole (N₁O₁), benzisoxazole (N₁O₁), benzodioxole (O₂), benzofurazan (N₂O₁), benzotriazole (N₃), benzothiofuran (S₁),
10 benzothiazole (N₁S₁), benzothiadiazole (N₂S);

C₁₀ (with 2 fused rings) derived from chromene (O₁), isochromene (O₁), chroman (O₁), isochroman (O₁), benzodioxan (O₂), quinoline (N₁), isoquinoline (N₁), quinolizine (N₁), benzoxazine (N₁O₁), benzodiazine (N₂), pyridopyridine (N₂),
15 quinoxaline (N₂), quinazoline (N₂), cinnoline (N₂), phthalazine (N₂), naphthyridine (N₂), pteridine (N₄);

C₁₁ (with 2 fused rings) derived from benzodiazepine (N₂);

C₁₃ (with 3 fused rings) derived from carbazole (N₁),
20 dibenzofuran (O₁), dibenzothiophene (S₁), carboline (N₂), perimidine (N₂), pyridoindole (N₂); and,

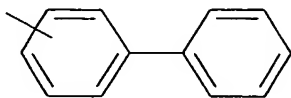
C₁₄ (with 3 fused rings) derived from acridine (N₁), xanthene (O₁), thioxanthene (S₁), oxanthrene (O₂), phenoxathiin (O₁S₁), phenazine (N₂), phenoxazine (N₁O₁),
25 phenothiazine (N₁S₁), thianthrene (S₂), phenanthridine (N₁), phenanthroline (N₂), phenazine (N₂).

If a heteroaryl or heterocyclyl group contains a nitrogen ring atom, this ring atom, where possible, may be in a
30 oxidised state, as an N-oxide.

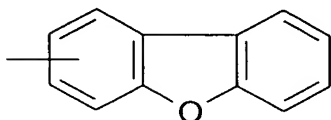
R³ is defined above as an optionally substituted C₆ aryl group linked to a further optionally substituted C₆ aryl group, wherein if both C₆ aryl groups are benzene rings ,

there may be an oxygen bridge between the two rings, bound adjacent the link on both rings. Thus, if both C₆ aryl groups are benzene rings, then R³ can be optionally substituted biphenyl:

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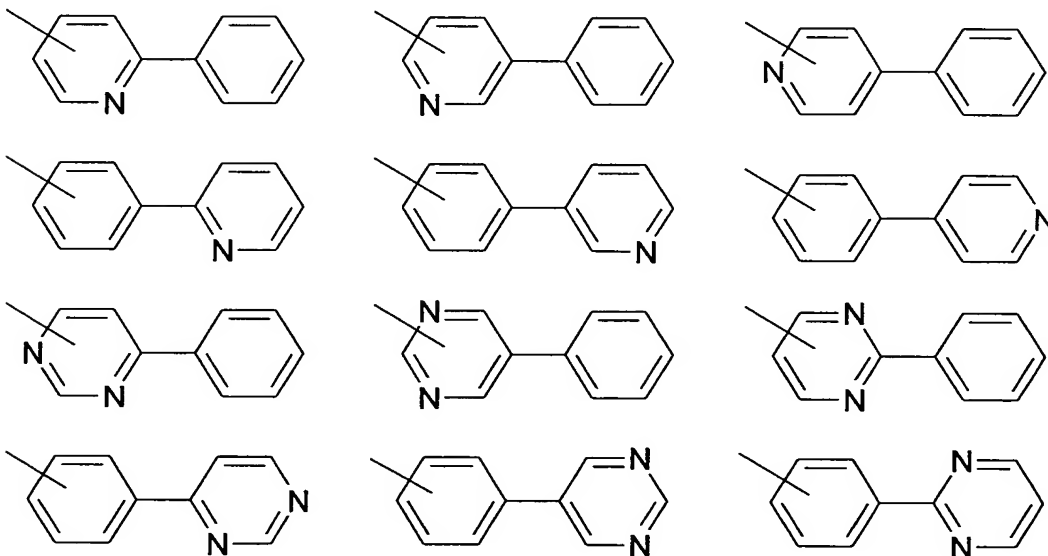
or optionally substituted dibenzofuran:



10

If one of the C₆ aryl groups is a C₆ heteroaryl group, then examples of R³ include, but are not limited to (not showing optional substitution):

15



The above groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves, the additional monodentate substituents listed below and alkoxylenes.

20

Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example,
5 a C₁₋₇ alkyl group (also referred to as a C₁₋₇ alkoxy group,
discussed below), a C₃₋₂₀ heterocyclyl group (also referred
to as a C₃₋₂₀ heterocyclyloxy group), or a C₅₋₂₀ aryl group
(also referred to as a C₅₋₂₀ aryloxy group), preferably a C₁₋₇
alkyl group.

10 C₁₋₇ alkoxy: -OR, wherein R is a C₁₋₇ alkyl group. Examples
of C₁₋₇ alkoxy groups include, but are not limited to, -OMe
(methoxy), -OEt (ethoxy), -O(nPr) (n-propoxy), -O(iPr)
(isopropoxy), -O(nBu) (n-butoxy), -O(sBu) (sec-butoxy),
15 -O(iBu) (isobutoxy), and -O(tBu) (tert-butoxy).

Oxo (keto, -one): =O.

Thione (thioketone): =S.

20 Imino (imine): =NR, wherein R is an imino substituent, for
example, hydrogen, C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl
group, or a C₅₋₂₀ aryl group, preferably hydrogen or a C₁₋₇
alkyl group. Examples of imino groups include, but are not
25 limited to, =NH, =NMe, =NEt, and =NPh.

Formyl (carbaldehyde, carboxaldehyde): -C(=O)H.

30 Acyl (keto): -C(=O)R, wherein R is an acyl substituent, for
example, a C₁₋₇ alkyl group (also referred to as C₁₋₇
alkylacyl or C₁₋₇ alkanoyl), a C₃₋₂₀ heterocyclyl group (also
referred to as C₃₋₂₀ heterocyclylacyl), or a C₅₋₂₀ aryl group
(also referred to as C₅₋₂₀ arylacyl), preferably a C₁₋₇ alkyl
group. Examples of acyl groups include, but are not limited

to, -C(=O)CH_3 (acetyl), $\text{-C(=O)CH}_2\text{CH}_3$ (propionyl),
 $\text{-C(=O)C(CH}_3)_3$ (t-butyl), and -C(=O)Ph (benzoyl, phenone).

Carboxy (carboxylic acid): -C(=O)OH .

5

Thiocarboxy (thiocarboxylic acid): -C(=S)SH .

Thiolocarboxy (thiolocarboxylic acid): -C(=O)SH .

10 Thionocarboxy (thionocarboxylic acid): -C(=S)OH .

Imidic acid: -C(=NH)OH .

Hydroxamic acid: -C(=NOH)OH .

15

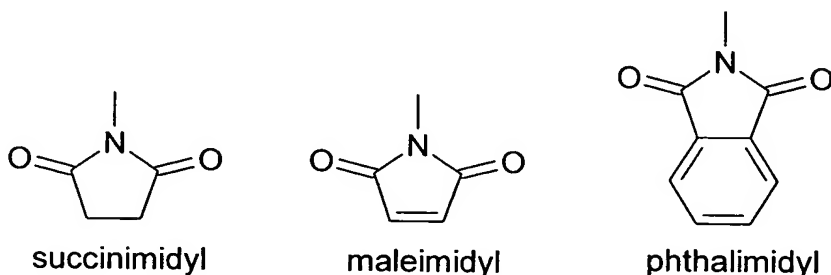
Ester (carboxylate, carboxylic acid ester, oxycarbonyl):
 -C(=O)OR , wherein R is an ester substituent, for example, a
 C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl
group, preferably a C_{1-7} alkyl group. Examples of ester
20 groups include, but are not limited to, -C(=O)OCH_3 ,
 $\text{-C(=O)OCH}_2\text{CH}_3$, $\text{-C(=O)OC(CH}_3)_3$, and -C(=O)OPh .

Acyloxy (reverse ester): -OC(=O)R , wherein R is an acyloxy
substituent, for example, a C_{1-7} alkyl group, a C_{3-20}
25 heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7}
alkyl group. Examples of acyloxy groups include, but are
not limited to, -OC(=O)CH_3 (acetoxy), $\text{-OC(=O)CH}_2\text{CH}_3$,
 $\text{-OC(=O)C(CH}_3)_3$, -OC(=O)Ph , and $\text{-OC(=O)CH}_2\text{Ph}$.

30 Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide):
 $\text{-C(=O)NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino
substituents, as defined for amino groups. Examples of
amido groups include, but are not limited to, -C(=O)NH_2 ,
 -C(=O)NHCH_3 , $\text{-C(=O)N(CH}_3)_2$, $\text{-C(=O)NHCH}_2\text{CH}_3$, and

-C(=O)N(CH₂CH₃)₂, as well as amido groups in which R¹ and R², together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl,
 5 thiomorpholinocarbonyl, and piperazinocarbonyl.

Acylamido (acylamino): -NR¹C(=O)R², wherein R¹ is an amide substituent, for example, hydrogen, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably
 10 hydrogen or a C₁₋₇ alkyl group, and R² is an acyl substituent, for example, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably hydrogen or a C₁₋₇ alkyl group. Examples of acylamide groups include, but are not limited to, -NHC(=O)CH₃,
 15 -NHC(=O)CH₂CH₃, and -NHC(=O)Ph. R¹ and R² may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:



20 Thioamido (thiocarbamyl): -C(=S)NR¹R², wherein R¹ and R² are independently amino substituents, as defined for amino groups. Examples of thioamido groups include, but are not limited to, -C(=S)NH₂, -C(=S)NHCH₃, -C(=S)N(CH₃)₂, and -C(=S)NHCH₂CH₃.

25

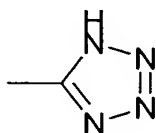
Ureido: -N(R¹)CONR²R³ wherein R² and R³ are independently amino substituents, as defined for amino groups, and R¹ is a ureido substituent, for example, hydrogen, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group,

preferably hydrogen or a C₁₋₇ alkyl group. Examples of ureido groups include, but are not limited to, -NHCONH₂, -NHCONHMe, -NHCONHEt, -NHCONMe₂, -NHCONEt₂, -NMeCONH₂, -NMeCONHMe, -NMeCONHEt, -NMeCONMe₂, and -NMeCONEt₂.

5

Guanidino: -NH-C(=NH)NH₂.

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



10

Amino: -NR¹R², wherein R¹ and R² are independently amino substituents, for example, hydrogen, a C₁₋₇ alkyl group (also referred to as C₁₋₇ alkylamino or di-C₁₋₇ alkylamino), a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably H or a C₁₋₇ alkyl group, or, in the case of a "cyclic" amino group, R¹ and R², taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Amino groups may be primary (-NH₂), secondary (-NHR¹), or tertiary (-NHR¹R²), and in cationic form, may be quaternary (-⁺NR¹R²R³). Examples of amino groups include, but are not limited to, -NH₂, -NHCH₃, -NHC(CH₃)₂, -N(CH₃)₂, -N(CH₂CH₃)₂, and -NHPh. Examples of cyclic amino groups include, but are not limited to, aziridino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, and thiomorpholino.

Amidine (amidino): -C(=NR)NR₂, wherein each R is an amidine substituent, for example, hydrogen, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably H or a C₁₋₇ alkyl group. Examples of amidine groups include,

30

but are not limited to, $-C(=NH)NH_2$, $-C(=NH)NMe_2$, and $-C(=NMe)NMe_2$.

Nitro: $-NO_2$.

5

Nitroso: $-NO$.

Cyano (nitrile, carbonitrile): $-CN$.

10 Sulfhydryl (thiol, mercapto): $-SH$.

Thioether (sulfide): $-SR$, wherein R is a thioether substituent, for example, a C_{1-7} alkyl group (also referred to as a C_{1-7} alkylthio group), a C_{3-20} heterocyclyl group, or a
15 C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of C_{1-7} alkylthio groups include, but are not limited to, $-SCH_3$ and $-SCH_2CH_3$.

Disulfide: $-SS-R$, wherein R is a disulfide substituent, for
20 example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group (also referred to herein as C_{1-7} alkyl disulfide). Examples of C_{1-7} alkyl disulfide groups include, but are not limited to, $-SSCH_3$ and $-SSCH_2CH_3$.

25

Sulfine (sulfinyl, sulfoxide): $-S(=O)R$, wherein R is a sulfine substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfine groups include, but are
30 not limited to, $-S(=O)CH_3$ and $-S(=O)CH_2CH_3$.

Sulfone (sulfonyl): $-S(=O)_2R$, wherein R is a sulfone substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7}

alkyl group, including, for example, a fluorinated or perfluorinated C₁₋₇ alkyl group. Examples of sulfone groups include, but are not limited to, -S(=O)₂CH₃ (methanesulfonyl, mesyl), -S(=O)₂CF₃ (triflyl), -S(=O)₂CH₂CH₃ (esyl), -S(=O)₂C₄F₉ (nonafllyl), -S(=O)₂CH₂CF₃ (tresyl),
5 -S(=O)₂CH₂CH₂NH₂ (tauryl), -S(=O)₂Ph (phenylsulfonyl, besyl), 4-methylphenylsulfonyl (tosyl), 4-chlorophenylsulfonyl (closyl), 4-bromophenylsulfonyl (brosyl), 4-nitrophenyl (nosyl), 2-naphthalenesulfonate (napsyl), and
10 5-dimethylamino-naphthalen-1-ylsulfonate (dansyl).

Sulfinic acid (sulfino): -S(=O)OH, -SO₂H.

15 Sulfonic acid (sulfo): -S(=O)₂OH, -SO₃H.

Sulfinate (sulfinic acid ester): -S(=O)OR; wherein R is a sulfinate substituent, for example, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably a C₁₋₇ alkyl group. Examples of sulfinate groups include, but
20 are not limited to, -S(=O)OCH₃ (methoxysulfinyl; methyl sulfinate) and -S(=O)OCH₂CH₃ (ethoxysulfinyl; ethyl sulfinate).

Sulfinyloxy: -OS(=O)R, wherein R is a sulfinyloxy
25 substituent, for example, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably a C₁₋₇ alkyl group. Examples of sulfinyloxy groups include, but are not limited to, -OS(=O)CH₃ and -OS(=O)CH₂CH₃.

30 Sulfamyl (sulfamoyl; sulfinic acid amide; sulfinamide): -S(=O)NR¹R², wherein R¹ and R² are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to, -S(=O)NH₂,

$-S(=O)NH(CH_3)$, $-S(=O)N(CH_3)_2$, $-S(=O)NH(CH_2CH_3)$,
 $-S(=O)N(CH_2CH_3)_2$, and $-S(=O)NHPh$.

Sulfonamido (sulfinamoyl; sulfonic acid amide; sulfonamide):

5 $-S(=O)_2NR^1R^2$, wherein R^1 and R^2 are independently amino
substituents, as defined for amino groups. Examples of
sulfonamido groups include, but are not limited to,
 $-S(=O)_2NH_2$, $-S(=O)_2NH(CH_3)$, $-S(=O)_2N(CH_3)_2$, $-S(=O)_2NH(CH_2CH_3)$,
 $-S(=O)_2N(CH_2CH_3)_2$, and $-S(=O)_2NHPh$.

10

Sulfonamino: $-NR^1S(=O)_2R$, wherein R^1 is an amino substituent,
as defined for amino groups, and R is a sulfonamino
substituent, for example, a C_{1-7} alkyl group, a C_{3-20}
heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7}
15 alkyl group. Examples of sulfonamino groups include, but
are not limited to, $-NHS(=O)_2CH_3$ and $-N(CH_3)S(=O)_2C_6H_5$.

Sulfinamino: $-NR^1S(=O)R$, wherein R^1 is an amino substituent,
as defined for amino groups, and R is a sulfinamino

20 substituent, for example, a C_{1-7} alkyl group, a C_{3-20}
heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7}
alkyl group. Examples of sulfinamino groups include, but
are not limited to, $-NHS(=O)CH_3$ and $-N(CH_3)S(=O)C_6H_5$.

25 As already mentioned, the above described groups may be
substituted, and particular examples include, but are not
limited to, C_{3-20} aryl- C_{1-7} alkyl groups, which include benzyl
(phenylmethyl, $PhCH_2-$), benzhydryl (Ph_2CH-), trityl
(triphenylmethyl, Ph_3C-), phenethyl (phenylethyl,
30 $Ph-CH_2CH_2-$), styryl ($Ph-CH=CH-$) and cinnamyl ($Ph-CH=CH-CH_2-$).

Bidentate groups

(i.e. groups with two points of covalent attachment; linking groups)

Alkylene: The term "C₁₋₃ alkylene", as used herein, pertains to a bidentate moiety obtained by removing two hydrogen atoms from each of two different carbon atoms, of a linear hydrocarbon compound having from 1 to 3 carbon atoms, which may be saturated or unsaturated. Thus, the term "alkylene" includes the sub-classes alkenylene and alkynylene.

In this context, the prefix C₁₋₃ denotes the number of carbon atoms, or range of number of carbon atoms.

Examples of saturated C₁₋₃ alkylene groups include -CH₂- (methylene), -CH₂CH₂- (ethylene) and -CH₂CH₂CH₂- (propylene).

Examples of unsaturated C₁₋₃ alkylene groups (which may be termed "C₂₋₃ alkenylene" or "C₂₋₃ alkynylene", as appropriate) include -CH=CH- (vinylene), -CH=CH-CH₂-, -CH₂-CH=CH-, -C≡C-, -C≡C-CH₂- and -CH₂-C≡C-.

The C₁₋₃ alkylene group may be substituted by any monodentate substituent described above.

Alkoxylenes: The term "alkoxylenes," as used herein, pertains to a bidentate group of formula -O(CH₂)_nO-, where n is 1 or 2.

Includes Other Forms

Unless otherwise specified, included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form (-COO⁻), a salt or solvate thereof, as well as conventional

protected forms. Similarly, a reference to an amino group includes the protonated form ($-N^+HR^1R^2$), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group.

5 Similarly, a reference to a hydroxyl group also includes the anionic form ($-O^-$), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

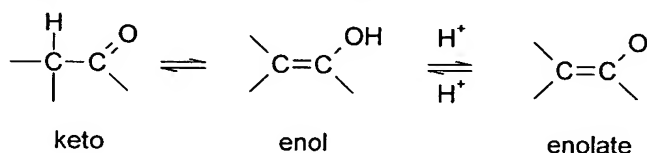
Isomers, Salts, Solvates and Protected Forms

10 Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms;
15 R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α - and β -forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof,
20 hereinafter collectively referred to as "isomers" (or "isomeric forms").

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers", as used
25 herein, are structural (or constitutional) isomers (i.e. isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a
30 hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class

(e.g. C₁₋₇alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

- 5 The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, 10 N-nitroso/hydroxyazo, and nitro/aci-nitro.



- Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For 15 example, H may be in any isotopic form, including ¹H, ²H (D), and ³H (T); C may be in any isotopic form, including ¹²C, ¹³C, and ¹⁴C; O may be in any isotopic form, including ¹⁶O and ¹⁸O; and the like.

- 20 Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g. asymmetric synthesis) and separation (e.g. fractional crystallisation and 25 chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

- Unless otherwise specified, a reference to a particular 30 compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge, et
5 *al.*, *J. Pharm. Sci.*, **66**, 1-19 (1977).

For example, if the compound is anionic, or has a functional group which may be anionic (e.g. -COOH may be -COO^-), then a salt may be formed with a suitable cation. Examples of
10 suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+ , alkaline earth cations such as Ca^{2+} and Mg^{2+} , and other cations such as Al^{+3} . Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e. NH_4^+) and substituted
15 ammonium ions (e.g. NH_3R^+ , NH_2R_2^+ , NHR_3^+ , NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine,
20 choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $\text{N}(\text{CH}_3)_4^+$.

If the compound is cationic, or has a functional group which
25 may be cationic (e.g. -NH_2 may be -NH_3^+), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric,
30 nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetoxybenzoic, acetic, ascorbic, aspartic, benzoic,

camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, 5 methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, 10 those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The 15 term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

20 It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in 25 which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g. pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, 30 which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive

functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A wide variety of such "protecting", "blocking", or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH₃, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R-CH(OR)₂) or ketal (R₂C(OR)₂), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C(OR)₂), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by

hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example,
5 as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example,
as: an acetamide (-NHCO-CH₃); a benzyloxy amide (-NHCO-
OCH₂C₆H₅, -NH-Cbz); as a t-butoxy amide (-NHCO-OC(CH₃)₃,
-NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-
OC(CH₃)₂C₆H₄C₆H₅, -NH-Bpoc), as a 9-fluorenylmethoxy amide
10 (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a
2-trimethylsilyl ethyloxy amide (-NH-Teoc), as a 2,2,2-
trichloroethyloxy amide (-NH-Troc), as an allyloxy amide
(-NH-Alloc), as a 2(-phenylsulfonyl)ethyloxy amide
(-NH-Psec); or, in suitable cases (e.g., cyclic amines), as
15 a nitroxide radical (>N-O·).

For example, a carboxylic acid group may be protected as an
ester for example, as: an C₁₋₇ alkyl ester (e.g., a methyl
ester; a t-butyl ester); a C₁₋₇ haloalkyl ester (e.g., a C₁₋₇
20 trihaloalkyl ester); a triC₁₋₇ alkylsilyl-C₁₋₇ alkyl ester; or
a C₅₋₂₀ aryl-C₁₋₇ alkyl ester (e.g. a benzyl ester; a
nitrobenzyl ester); or as an amide, for example, as a methyl
amide.

25 For example, a thiol group may be protected as a thioether
(-SR), for example, as: a benzyl thioether; an
acetamidomethyl ether (-S-CH₂NHC(=O)CH₃).

The term "treatment", as used herein in the context of
30 treating a condition, pertains generally to treatment and
therapy, whether of a human or an animal (e.g. in veterinary
applications), in which some desired therapeutic effect is
achieved, for example, the inhibition of the progress of the
condition, and includes a reduction in the rate of progress,

a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e. prophylaxis) is also included.

5 The term "therapeutically-effective amount", as used herein, pertains to that amount of an active compound, or a material, composition or dosage form comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable
10 benefit/risk ratio, when administered in accordance with a desired treatment regimen. Suitable dose ranges will typically be in the range of from 0.01 to 20 mg/kg/day, preferably from 0.1 to 10 mg/kg/day.

15 **Compositions and their administration**

Compositions may be formulated for any suitable route and means of administration. Pharmaceutically acceptable carriers or diluents include those used in formulations suitable for oral, rectal, nasal, topical (including buccal
20 and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of
25 pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid
30 carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

For solid compositions, conventional non-toxic solid carriers include, for example, pharmaceutical grades of

mannitol, lactose, cellulose, cellulose derivatives, starch, magnesium stearate, sodium saccharin, talcum, glucose, sucrose, magnesium carbonate, and the like may be used. The active compound as defined above may be formulated as

5 suppositories using, for example, polyalkylene glycols, acetylated triglycerides and the like, as the carrier. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc, an active compound as defined above and optional pharmaceutical

10 adjuvants in a carrier, such as, for example, water, saline aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such

15 as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those

20 skilled in this art; for example, see Remington's Pharmaceutical Sciences, 20th edition, pub. Lippincott, Williams & Wilkins, 2000. The composition or formulation to be administered will, in any event, contain a quantity of the active compound(s) in an amount effective to alleviate

25 the symptoms of the subject being treated.

Dosage forms or compositions containing active ingredient in the range of 0.25 to 95% with the balance made up from non-toxic carrier may be prepared.

30

For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, cellulose,

cellulose derivatives, sodium crosscarmellose, starch, magnesium stearate, sodium saccharin, talcum, glucose, sucrose, magnesium carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions may contain 1%-95% active ingredient, more preferably 2-50%, most preferably 5-8%.

Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol or the like. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, triethanolamine sodium acetate, etc.

The percentage of active compound contained in such parental compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject. However, percentages of active ingredient of 0.1% to 10% in solution are employable, and will be higher if the composition is a solid which will be subsequently diluted to the above percentages. Preferably, the composition will comprise 0.2-2% of the active agent in solution.

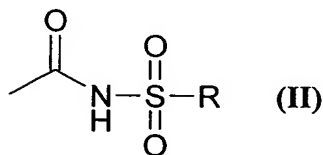
Acronyms

For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), n-propyl (nPr), iso-propyl (iPr), n-butyl (nBu), sec-butyl (sBu), iso-butyl (iBu), tert-butyl (tBu), n-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh), benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

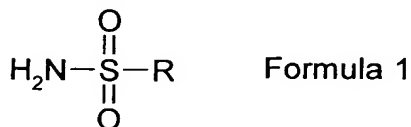
For convenience, many chemical compounds are represented using well known abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), iso-propanol (i-PrOH), methyl ethyl ketone (MEK), ether or diethyl ether (Et₂O), acetic acid (AcOH), dichloromethane (methylene chloride, DCM), acetonitrile (ACN), trifluoroacetic acid (TFA), dimethylformamide (DMF), tetrahydrofuran (THF), and dimethylsulfoxide (DMSO).

General Synthesis Methods

Compounds of the invention wherein R⁵ is of formula (II):

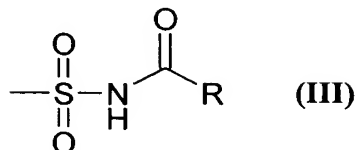


may be synthesised from the analogous compound of the invention wherein R⁵ is carboxy, by reaction with a compound of formula 1:

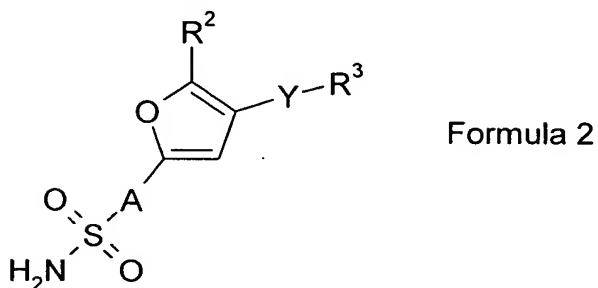


in basic conditions, preferably aided by a coupling agent, for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

Compounds of the invention wherein R⁵ is of formula (III):



may be synthesized from a compound of formula 2:

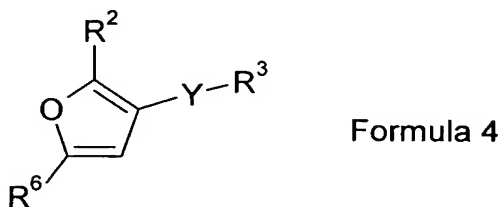


by reaction with a compound of formula 3:

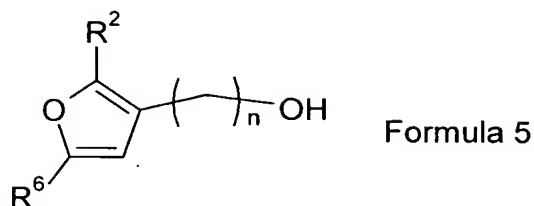


wherein X is either OH or halo, where if X is OH, the use of basic conditions and a coupling agent is preferred.

Compounds of formulae (I) and 2, or where the group -A-R⁵ is present as a precursor or protected form, may be represented as compounds of formula 4:



where R⁶ is -A-R⁵ or its precursor or protected form. The protecting groups used may be conventional, or the group may be resin-bound. If Y is -(CH₂)_n-O- or -(CH₂)_n-S-, then these compounds can be synthesised from compounds of formula 5:



by one of two possible routes.

In the first route, a compound of formula 6:



, where X' is S or O, is coupled to a compound of formula 5 using the Mitsunobu reaction, for example by treatment with triphenyl phosphine (Ph_3P) and diisopropylazodicarboxylate (DIAD).

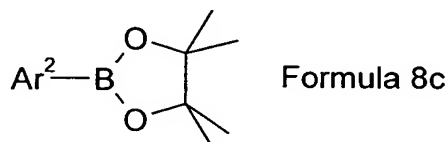
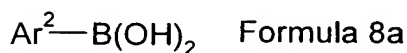
10

The second route is a two stage route, the first stage being the Mitsunobu coupling of a compound of formula 7a:



wherein Ar^1 is the first C_6 aryl component of R^3 and Hal is I or Br followed by a Suzuki coupling of a compound of formula 8a (or equivalent ester of formula 8c):

15

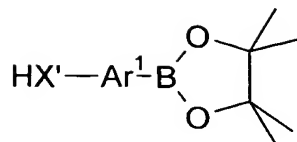
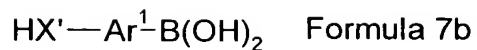


20

wherein Ar^2 is the second C_6 aryl component of R^3 . The Suzuki coupling may be achieved using, for example, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) as the palladium catalyst.

This route may also be 'reversed' such that the Mitsunobu coupling is of a boronic acid of formula 7b (or preferably equivalent ester of formula 7c):

25



Formula 7c

wherein Ar^1 is the first C_6 aryl component of R^3 , followed by a Suzuki coupling of a compound of formula 8b:



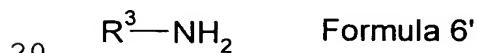
- 5 wherein Ar^2 is the second C_6 aryl component of R^3 and Hal is I or Br.

If the compound of formula 7b or 7c is not readily available then a compound of formula 7d:

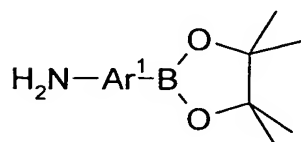
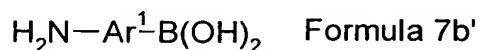


may be coupled, followed by conversion of the bromo group to the required boronic acid or ester.

- 15 Compounds of formula 4 where Y is $-(\text{CH}_2)_n-\text{NH}-$ can also be synthesized from compounds of formula 5. In one method, the alcohols of formula 5 are oxidized to the corresponding aldehyde, for example using the Dess-Martin reagent, followed by reductive coupling to an amine, which may be of formula 6':



or of formula 7a', 7b' or 7c':

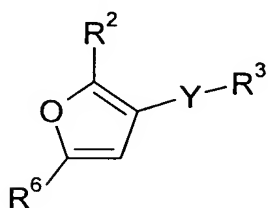


Formula 7c'

- 25 for subsequent Suzuki coupling. The reductive coupling can be carried out using sodium cyanoborohydride.

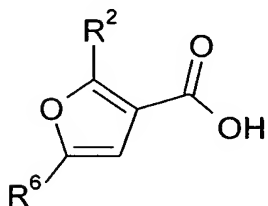
In another method, the alcohol of formula 5 is converted to the corresponding halide, using a halogenating reagent , for example conversion to chlorine using 4-methyl-benzene sulfonyl chloride, followed by coupling to an amine which may be of formula 6', or of formula 7a', 7b' or 7c' for subsequent Suzuki coupling. The amine coupling is carried out in the presence of potassium iodide, or equivalent reagents. This method can also be used to couple alcohols and thiols of formulae 6, 7a, 7b and 7d, where X' is O or S.

Compounds of formula 4:



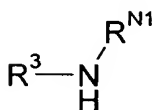
Formula 4

where Y is $-C(=O)-NR^{N1}-$ may be synthesised from a compound of formula 9:



Formula 9

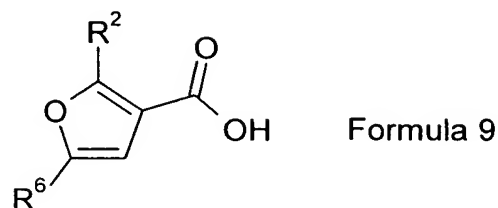
by reaction with a amine of formula 10:



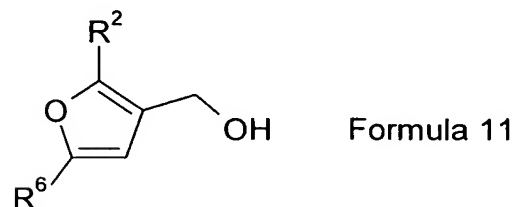
Formula 10

in basic conditions, preferably with the aid of a coupling agent.

Compounds of formula 9:

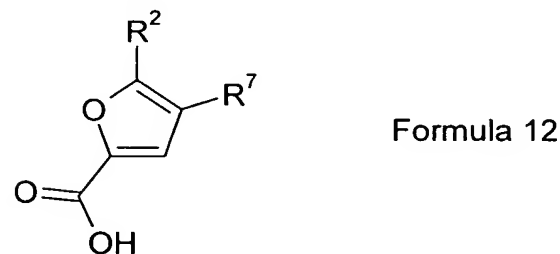


may be derived from compounds of formula 11:

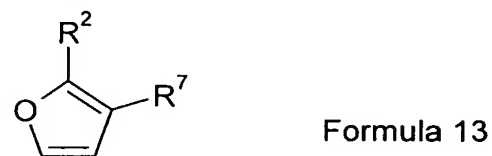


5 by oxidation, for example, using Jones' reagent.

Compounds of formula (I) where A is a single bond, and R⁵ is carboxy, and compounds where the group -Y-R³ is present as a precursor or protected form, may be represented as compounds
10 of formula 12:



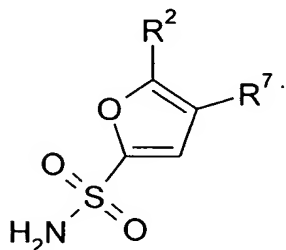
where R⁷ is -Y-R³ or its precursor or protected form. These compounds may be synthesised from compounds of formula 13:



15 by treatment with n-butyllithium, followed by carbon dioxide at low temperatures.

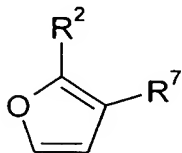
In a similar fashion, compounds of formula 2 where A is a single bond, and R⁵ is carboxy, and compounds where the

group $-Y-R^3$ is present as a precursor or protected form, may be represented as compounds of formula 14:



Formula 14

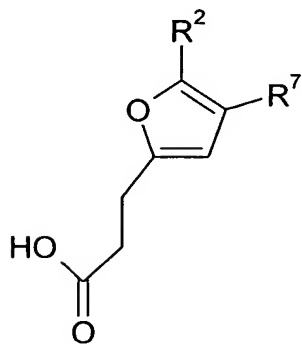
where R^7 is $-Y-R^3$ or its precursor or protected form. These compounds may be synthesised from compounds of formula 13:



Formula 13

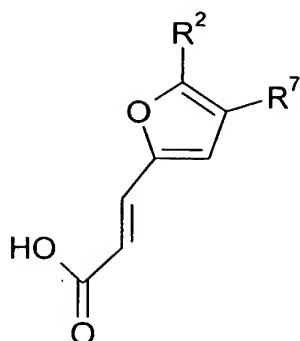
by treatment with a strong base and sulphur dioxide at low temperatures, followed by amination.

10 Compounds of formula (I) where A is a $-C_2H_4-$, and R^5 is carboxy, and compounds where the group $-Y-R^3$ is present as a precursor or protected form, may be represented as compounds of formula 15:



Formula 15

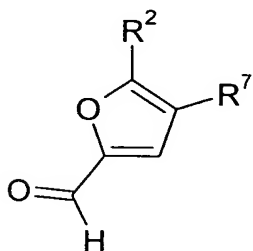
15 where R^7 is $-Y-R^3$ or its precursor or protected form. These compounds may be synthesised from compounds of formula 16:



Formula 16

by hydrogenation, using a palladium catalyst.

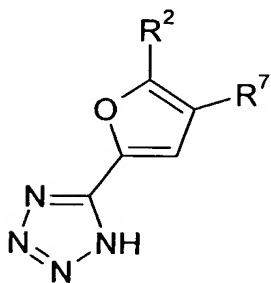
Compounds of formula 16 may be synthesised from compounds of
5 formula 17:



Formula 17

by the Wittig coupling of an acetic ester, using, for
example, triethylphosphonoacetate as the Wittig reagent,
followed by hydolysis under alkaline conditions, e.g.
10 lithium hydroxide in a suitable solvent, e.g. aqueous
alcohol.

Compounds of formula 17 may also be used to synthesise
compounds of formula 18:



Formula 18

15

where R² and R⁷ are as defined above. The reaction proceeds
via a cyano intermediate which may be obtained by treating

compounds of formula 17 with hydroxylamine to form the oxime derivative, which can be dehydrated to the cyano compound with, for example, 2-chloro-1,3-dimethylimidazolium chloride in the presence of a base. The cyano intermediate can be
5 converted into compounds of formula 18 by treatment with sodium azide, in the presence of a base.

Compounds where Y is $-(CH_2)_n-S(=O)-$ and $-(CH_2)_n-S(=O)_2-$ may be obtained from the corresponding compound where Y is $-(CH_2)_n-S-$ by oxidation with a peracid, for example 3-chloro-
10 benzenecarboperoxoic acid.

Compounds where Y is $-(CH_2)_n-NR^{N1}-$ may be obtained from the corresponding compound where Y is $-(CH_2)_n-NH-$ by direction
15 alkylation by $R^{N1}I$, in the presence of a weak base.

The starting materials described above are generally commercially available or synthesisable using known methods. For example, example 22A below describes a method of
20 synthesizing 2-substitued furans.

Some of the reaction steps described above may be carried out using resins, as is shown in the examples.

25 *Preferences*

The following preferences may be combined with one another, and may be different for each aspect of the present invention.

30 R^2 is preferably selected from H or an optionally substituted C_{1-3} alkyl group, more preferably H, methyl, CF_3 or iso-propyl, and most preferably R^2 is a methyl group.

Y is preferably $-(CH_2)_n-X-$, and n is preferably 1. X is

preferably O, S or NH, with NH being the most preferred. In some embodiments the preferred option for Y is $-\text{CH}_2-\text{O}-$.

If Y is $-\text{C}(=\text{O})\text{NR}^{\text{N}2}-$, then $\text{R}^{\text{N}2}$ is preferably selected from H,
5 and optionally substituted C_{1-4} alkyl, in particular Me.

The C_6 aryl groups of R^3 are preferably independently selected from those derived from benzene and heteroaryl groups, where the heteroatom or heteroatoms are nitrogen.
10 Most preferred are C_6 aryl groups derived from benzene, pyridine and 1,3-pyrimidine. It is further preferred that either both C_6 aryl groups are derived from benzene or that one group is derived from benzene and the other from pyridine or 1,3-pyrimidine, with pyridine being preferred,
15 especially as the aryl group furthest from the furan core.

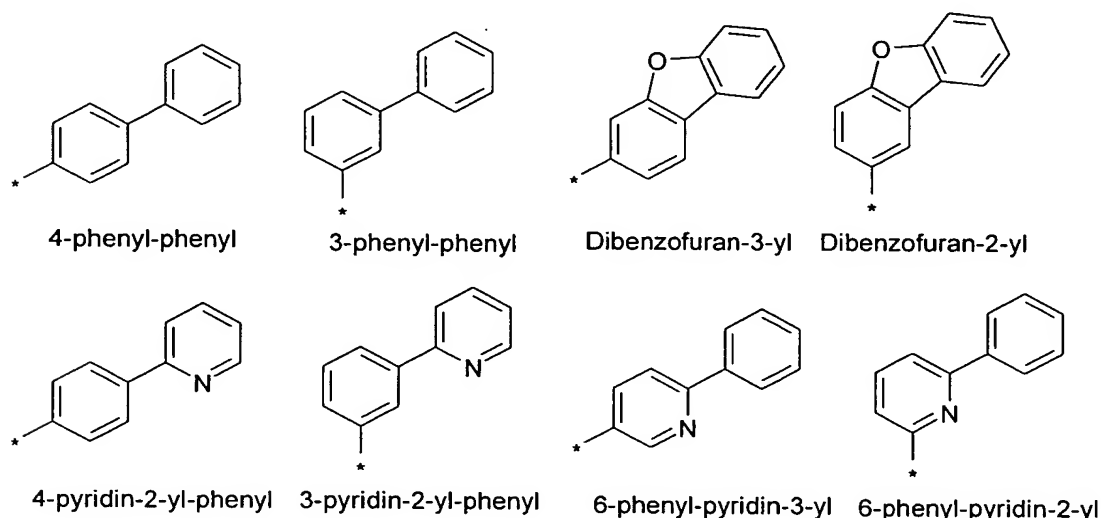
If both C_6 aryl groups are derived from benzene, it is preferred that there is not an oxygen bridge between the two rings, bound adjacent the link on both rings, i.e. that R_3
20 is optionally substituted biphenyl rather than optionally substituted dibenzofuranyl.

If one or more of the C_6 aryl groups is derived from pyridine, then it is preferred that the nitrogen ring atom
25 is adjacent the link between the two rings that make up the R^3 group.

If one or more of the C_6 aryl groups is derived from 1,3-pyrimidine, then it is preferred that the link between the
30 two rings that make up the R^3 group is between the two nitrogen atoms.

It is further preferred that that the single bond joining the two C_6 aryl groups is in the 4-position of the ring

bound to Y. Thus, 4-phenyl-phenyl is preferred to 3-phenyl-phenyl; dibenzofuran-3-yl is preferred to di-benzofuran-2-yl, 4-pyridin-2-yl-phenyl is preferred to 3-pyridin-2-yl-phenyl and 6-phenyl-pyridin-3-yl is preferred to 6-phenyl-pyridin-2-yl:



Both C₆ aryl groups of R³ are optionally substituted, although it is preferred that only the C₆ aryl group not bound to Y is substituted.

Preferred substituents on the C₆ aryls of R³ include, but are not limited to: optionally substituted C₁₋₇ alkyl groups, more preferably methyl and substituted C₁₋₄ alkyl groups, e.g. -CF₃, CH₂OH; C₁₋₇ alkoxy groups, more preferably C₁₋₄ alkoxy groups, e.g. -OMe, -OCF₃, -OEt, -OCHF₂; C₁₋₇ thioether group, more preferably C₁₋₄ thioether group, e.g. -SMe; amino groups, optionally substituted by one or two C₁₋₄ alkyl groups, e.g. -NMe₂; halo groups, more preferably -F or -Cl; cyano; alkoxy groups, more preferably -O-CH₂-O-; C₁₋₄ acyl groups, more preferably -C(=O)Me.

The preferred location for a substituent on the C₆ aryl group not bound to Y is para to the bond between the two C₆

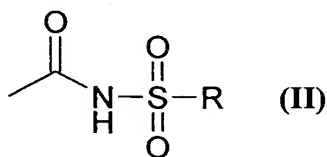
aryl groups, with the meta position being less preferred. Therefore, if R^3 is 4-phenyl-phenyl, the substituent is preferably at the 4'-position.

- 5 In some embodiments of the present invention A is preferably a single bond, whereas in other embodiments A is preferably a C_{1-3} alkylene group. In particular, when R^5 is carboxy, A is more preferably a C_{1-3} alkylene group, with vinylene being most preferred.

10

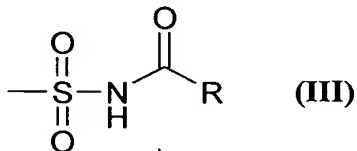
R^5 is preferably either:

- (i) a group of formula (II):



; or

- (ii) a group of formula (III):



15

with a group of formula (II) being more preferred.

The above preference for R^5 is particularly applicable when R^2 is methyl and Y is $-CH_2-O-$.

20

- Where R^5 is of formula (II) or (III), R is preferably selected from an optionally substituted C_{5-20} aryl group, and an optionally substituted C_{5-20} aryl- C_{1-7} alkyl group, wherein the C_{1-7} alkyl group is more preferably methyl. In these groups the C_{5-20} aryl group is preferably a heteroaryl group, itself preferably having a single aromatic ring. Such groups may preferably be substituted with C_{1-4} alkyl groups, such as methyl and hydroxy. Thus, preferred R groups
- 25

include, but are not limited to: phenyl; benzyl; 3,5,
dimethyl-isoxazol-4-yl; thiophen-2-yl; 5-methyl-pyridin-yl;
and 4-hydroxy-phenyl.

- 5 If R in formula (II) or (III) is a C₁₋₇ alkyl group, it is
more preferably a C₁₋₄ alkyl group, for example methyl or
propyl.

Particularly preferred compounds of the present invention
10 include:

4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
carboxylic acid (4);

N-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
carbonyl]-benzenesulfonamide (5);

- 15 N-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
carbonyl]-C-phenyl-methanesulfonamide (6);

N-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
carbonyl]-methanesulfonamide (7);

- 20 Propane-1-sulfonic acid [4-(4'-methoxy-biphenyl-4-
yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (8);

3,5-Dimethyl-isoxazole-4-sulfonic acid [4-(4'-methoxy-
biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide
(9);

- 25 Thiophene-2-sulfonic acid [4-(4'-methoxy-biphenyl-4-
yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (10);

5-Methyl-pyridyl-2-sulfonic acid [4-(4'-methoxy-biphenyl-4-
yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (11);

4-Aminomethyl-N-[4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-
methyl-furan-2-carbonyl]-benzenesulfonamide

- 30 (trifluoroacetate salt) (12);

4-Hydroxy-N-[4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-
furan-2-carbonyl]-benzenesulfonamide (13);

4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid

(18);

N-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-
benzenesulfonamide (19);

4-(4'-Acetyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
5 carboxylic acid (21);

N-[4-(4'-Acetyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
carbonyl]-benzenesulfonamide (22);

4-(4'-Methoxy-biphenyl-4-ylcarbamoyl)-5-methyl-furan-2-
carboxylic acid (24);

10 5-Benzenesulfonylaminocarbonyl-2-methyl-furan-3-carboxylic
acid (4'-methoxy-biphenyl-4-yl)-amide (25);

4-(4'-Chloro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
carboxylic acid (27);

4-(4-Benzo[1,3]dioxol-5-yl-phenoxy-methyl)-5-methyl-furan-2-
15 carboxylic acid (28);

[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acetic acid
(31);

4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-
acetic acid (32);

20 3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionic
acid (37);

N-{3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-
propionyl}-benzene sulfonamide (38);

3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
25 yl]-propionic acid (39);

N-{3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-
2-yl]-propionyl}-benzene sulfonamide (40);

3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acrylic
acid (42);

30 3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
yl]-acrylic acid (43);

- 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid
benzoylamide (46);
- 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
sulfonic acid benzoylamide (49);
- 5 4-(Dibenzofuran-3-yloxymethyl)-5-methyl-furan-2-carboxylic
acid (50);
- 4-[4-(5-Methoxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-
2-carboxylic acid (53);
- 4-[6-(4-Methoxy-phenyl)-pyridin-3-yloxymethyl]-5-methyl-
10 furan-2-carboxylic acid (56);
- 4-(4'-Cyano-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
carboxylic acid (57);
- 3-Morpholin-4-yl-propane-1-sulphonic acid [4-(4'-methoxy-
biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide
15 (59);
- N-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-2-
methyl-benzenesulphonamide (60);
- 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid
butyryl-amide (61);
- 20 4-(Biphenyl-4-yloxymethyl)-5-methyl
-furan-2-sulfonic acid phenylacetyl-amide (62);
- 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid
(3,5-dimethyl-isoxazole-4-carbonyl)-amide (63);
- 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid
25 (thiophene-2-carbonyl)-amide (64);
- 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid
(3-methoxy-propionyl)-amide (65);
- 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid
(pyridin-3-yl-acetyl)-amide (66);
- 30 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid
(pyridine-4-carbonyl)-amide (67);
- 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid
(pyridine-3-carbonyl)-amide (68);

- 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid (3,5-dimethyl-isoxazole-4-carbonyl)-amide (69);
- 4-[2-(Biphenyl-4-yloxy)-ethyl]-5-methyl-furan-2-carboxylic acid (72);
- 4-[2-(4'-Methoxy-biphenyl-4-yloxy)-ethyl]-5-methyl-furan-2-carboxylic acid (73);
- 4-[2-(Dibenzofuran-3-yloxy)-ethyl]-5-methyl-furan-2-carboxylic acid (74);
- 4-(Biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (77);
- 4-(Dibenzofuran-2-yloxymethyl)-furan-2-carboxylic acid (78);
- 4-(4'-Cyano-biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (79);
- 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (80);
- 4-(Dibenzofuran-3-yloxymethyl)-furan-2-carboxylic acid (81);
- 4-(Biphenyl-4-yloxymethyl)-5-isopropyl-furan-2-carboxylic acid (85);
- 5-Isopropyl-4-(4'-methoxy-biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (86);
- 4-(Dibenzofuran-3-yloxymethyl)-5-isopropyl-furan-2-carboxylic acid (87);
- 4-(Biphenyl-4-yloxymethyl)-5-trifluoromethyl-furan-2-carboxylic acid (90);
- 4-(Biphenyl-3-yloxymethyl)-5-trifluoromethyl-furan-2-carboxylic acid (91);
- 4-(Dibenzofuran-2-yloxymethyl)-5-trifluoromethyl-furan-2-carboxylic acid (92);
- 4-(4'-Cyano-biphenyl-4-yloxymethyl)-5-trifluoromethyl-furan-2-carboxylic acid (93);
- 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-trifluoromethyl-furan-2-carboxylic acid (94);
- 4-(Dibenzofuran-3-yloxymethyl)-5-trifluoromethyl-furan-2-

- carboxylic acid (95);
4-(3',4'-Dimethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
carboxylic acid (96);
4-(4'-Ethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
5 carboxylic acid (98);
4-(2'-Chloro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
carboxylic acid (99);
4-(2',6'-Difluoro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
carboxylic acid (100);
10 5-Methyl-4-(2'-trifluoromethyl-biphenyl-4-yloxymethyl)-
furan-2-carboxylic acid (102);
4-(3'-Fluoro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
carboxylic acid (104);
5-Methyl-4-(2'-methylsulfonyl-biphenyl-4-yloxymethyl)-furan-
15 2-carboxylic acid (105);
4-(3',4'-Dimethoxy-biphenyl-3-yloxymethyl)-5-methyl-furan-2-
carboxylic acid (108);
5-Methyl-4-(3'-trifluoromethyl-biphenyl-3-yloxymethyl)-
furan-2-carboxylic acid (109);
20 4-(4'-Hydroxymethyl-biphenyl-4-yloxymethyl)-5-methyl-furan-
2-carboxylic acid (110);
5-Methyl-4-(4'-methylsulfonyl-biphenyl-4-yloxymethyl)-furan-
2-carboxylic acid (111);
4-(3'-Hydroxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
25 carboxylic acid (112);
4-(4'-Dimethylamino-biphenyl-4-yloxymethyl)-5-methyl-furan-
2-carboxylic acid (113);
5-Methyl-4-(4'-trifluoromethoxy-biphenyl-4-yloxymethyl)-
furan-2-carboxylic acid (114);
30 5-Methyl-4-(2'-trifluoromethoxy-biphenyl-4-yloxymethyl)-
furan-2-carboxylic acid (115);
4-(3'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
carboxylic acid (116);

- 4-(3'-Acetyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (117);
- 4-(4'-Fluoro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (118);
- 5 N-4-(4'-Methoxy-biphen-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-dimethylaminosulphonamide (122);
- 4-(2'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (126);
- N-[4-(2'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (127);
- 10 4-(4'-Difluoromethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (129);
- N-[4-(4'-Difluoromethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (130);
- 15 3,5-Dimethyl-isoxazole-4-sulfonic acid [4-(4'-difluoromethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (131);
- N-{4-[4-(5-Methoxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-2-carbonyl}-benzenesulfonamide (132);
- 20 3,5-Dimethyl-isoxazole-4-sulfonic acid {4-[4-(5-methoxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-2-carbonyl}-amide (133);
- N-{4-[4-(5-Methoxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-2-carbonyl}-2-methyl-benzenesulfonamide (134);
- 25 N-{4-[4-(5-Methoxy-1-oxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-2-carbonyl}-benzenesulfonamide (135);
- 5-Methyl-4-(4-pyrimidin-2-yl-phenoxy-methyl)-furan-2-carboxylic acid (137);
- N-[5-Methyl-4-(4-pyrimidin-2-yl-phenoxy-methyl)-furan-2-carbonyl]-benzenesulfonamide (138);
- 30 4-(2',4'-Dimethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (140);
- N-[4-(2',4'-Dimethoxy-biphenyl-4-yloxymethyl)-5-methyl-

furan-2-carbonyl]-benzenesulfonamide (141);

3,5-Dimethyl-isoxazole-4-sulfonic acid [4-(2',4'-dimethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (142);

5 4-(4'-Methoxy-2'-methyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (144);

N-[4-(4'-Methoxy-2'-methyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (145);

10 3,5-Dimethyl-isoxazole-4-sulfonic acid [4-(4'-methoxy-2'-methyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (146);

5-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-1H-tetrazole (149);

15 4-(4'-Difluoromethoxy-biphenyl-4-ylsulfanylmethyl)-5-methyl-furan-2-carboxylic acid (153);

N-[4-(4'-Difluoromethoxy-biphenyl-4-ylsulfanylmethyl)-5-methyl-furan-2-carbonyl]-2-methyl-benzenesulfonamide (154);

N-[4-(4'-Difluoromethoxy-biphenyl-4-ylsulfanylmethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (155);

20 N-[4-(4'-Difluoromethoxy-biphenyl-4-sulfinylmethyl)-5-methyl-furan-2-carbonyl]-2-methyl-benzenesulfonamide (156);

N-[4-(4'-Difluoromethoxy-biphenyl-4-sulfonylmethyl)-5-methyl-furan-2-carbonyl]-2-methyl-benzenesulfonamide (156a);

25 4-(Biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carboxylic acid (160);

N-[4-(Biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (161);

N-[4-(Biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carbonyl]-2-methyl-benzenesulfonamide (162);

30 N-(4-{[4-(5-Methoxy-pyridin-2-yl)-phenylamino]-methyl}-5-methyl-furan-2-carbonyl)-2-methyl-benzenesulfonamide (167);

4-[(4'-Difluoromethoxy-biphenyl-4-ylamino)-methyl]-5-methyl-furan-2-carboxylic acid (171);

N-{4-[(4'-Difluoromethoxy-biphenyl-4-ylamino)-methyl]-5-methyl-furan-2-carbonyl}-benzenesulfonamide (**172**);
N-{4-[(4'-Difluoromethoxy-biphenyl-4-ylamino)-methyl]-5-methyl-furan-2-carbonyl}-2-methyl-benzenesulfonamide (**173**);
5 3,5-Dimethyl-isoxazole-4-sulfonic acid {4-[(4'-difluoromethoxy-biphenyl-4-ylamino)-methyl]-5-methyl-furan-2-carbonyl}-amide (**174**);
4-{[(4'-Difluoromethoxy-biphenyl-4-yl)-methyl-amino]-methyl}-5-methyl-furan-2-carboxylic acid (**176**); and
10 N-(4-{[(4'-Difluoromethoxy-biphenyl-4-yl)-methyl-amino]-methyl}-5-methyl-furan-2-carbonyl)-2-methyl-benzenesulfonamide (**177**).

The selectivity of the compound for antagonising EP₄
15 receptors over the other EP receptors (i.e. EP₁, EP₂, EP₃) can be quantified by dividing the K_i for EP₄ (see below) by the K_i for the other EP receptors (see below). The resulting ratio is preferably 10 or more, more preferably 100 or more.

Synthesis Examples

General Experimental Details

All reactions were carried out under an inert atmosphere of nitrogen.

25 Where products were purified by flash chromatography the stationary phase used was silica gel for chromatography, 0.035 to 0.070 mm (220 to 440 mesh) (e.g. Fluka silica gel 60). An applied pressure of nitrogen of ~10 psi was used to
30 accelerate column elution. Thin layer chromatography (TLC) was carried out on aluminium foil plates coated with silica gel containing a fluorescent indicator (254 nm) (e.g. Fluka 60778).

Petroleum ether refers to that fraction with a boiling point of 40-60°C.

Organic solutions were dried over magnesium sulphate unless
5 otherwise specified.

PS-TsCl refers to Polystyrene scavenger resin (loading 1.97 mmol/g) - Argonaut Technologies (P/N 800277)

10 *Preparative HPLC System*

Preparative HPLC was carried out on a C18-reverse-phase column (10 x 2.1 cm i.d Genesis column with 7 µm particle size), eluting with a gradient of acetonitrile (containing 0.1% trifluoroacetic acid) and water (containing 0.1%
15 trifluoroacetic acid) at a flow rate of 5 ml/min. UV detection at 230 nm was used unless otherwise stated.

LC/MS Systems

The Liquid Chromatography Mass Spectroscopy (LC/MS) systems
20 used are as follows.

LC/MS System A:

Mass Spectrometer - Platform LC with electrospray source operating in positive and negative Ion mode. HP1100 system running at 2.0 mL/min, 200 µL/min split
25 to the ESI source with inline HP1100 DAD detection and SEDEX ELS detection.

Mobile Phase

- 30 A) Water 0.1 % Formic Acid
B) acetonitrile 0.1% Formic Acid

Gradient

Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
0.50	2.0	95	5
4.50	2.0	5	95
5.00	2.0	5	95
5.50	2.0	95	5

Column - Luna 3u C18(2) 30x4.6mm

5 LC/MS System B:

Mass Spectrometer - Platform II with electrospray source operating in negative ion mode. HP1100 system running at 2.0 mL/min, 200 µL/min split to the ESI source with inline HP1100 DAD detection and SEDEX ELS detection.

10

Mobile Phase

A) Water 0.1 % Diethylamine

B) acetonitrile

15

Gradient

Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
0.50	2.0	95	5
4.00	2.0	5	95
4.50	2.0	5	95
5.00	2.0	95	5
20.00	2.0	95	5

Column - XTerra MS C18 3.5µm 4.6 x 30mm

LCMS System C:

Mass Spectrometer - Finnigan TSQ700 with electrospray source operating in negative ion mode.

HP1050 system running at 2.0 mL/min, 200 µL/min split to the ESI source with inline HP1050 Single wavelength UV detector at 254 nm.

Mobile Phase

A) Water 0.1 % Diethylamine

B) acetonitrile

Gradient

Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
1.00	2.0	95	5
15.00	2.0	5	95
17.00	2.0	5	95
18.00	2.0	95	5
20.00	2.0	95	5

Column - XTerra MS C18 3.5µm 4.6 x 30mm

LC/MS System D:

Mass Spectrometer - Finnigan TSQ700 with electrospray source operating in positive or negative ion mode.

HP1050 system running at 2.0 mL/min, 200 µL/min split to the ESI source with inline HP1050 Single Wavelength UV detector at 254 nm.

Mobile Phase

A) Water 0.1 % formic Acid

B) acetonitrile 0.1% formic Acid

Gradient			
Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
1.00	2.0	95	5
15.00	2.0	5	95
17.00	2.0	5	95
18.00	2.0	95	5
20.00	2.0	95	5

Column - Higgins Clipius C18 5µm 100 x 3.0mm

5 ¹H NMR system

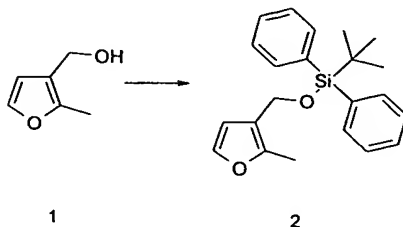
The ¹H NMR spectra were recorded on a Varian Unity Inova 400, which operates at 400 MHz for ¹H. It is equipped with a 5mm inverse detection triple resonance probe for detection of ¹H. The magnetic field is provided by a 9.4 Tesla Oxford instruments super-conducting magnet. The host computer is a Sun Microsystems SunBlade 1000 workstation. D₆-dimethylsulphoxide was used as solvent unless stated otherwise. Tetramethylsilane was used as internal standard. Coupling constants are reported in Hz.

15

Example 1: Synthesis of 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (4), 4-(Dibenzofuran-3-yloxymethyl)-5-methyl-furan-2-carboxylic acid (50), 4-(Dibenzofuran-2-yloxymethyl)-5-methyl-furan-2-carboxylic acid (56) and 4-(4'-Cyano-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (57)

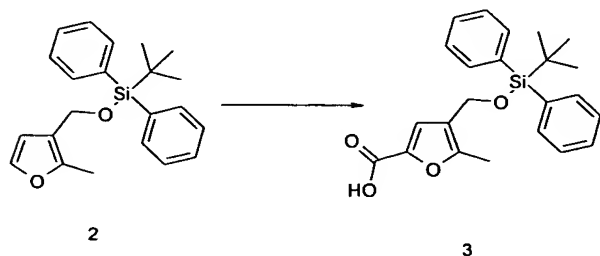
20

(a) 3-(*tert*-Butyl-diphenyl-silanyloxymethyl)-2-methyl-furan
(2)



5 A stirred solution of (2-methyl-3-furan-3-yl)-methanol
(1) (31.87 g) in N,N-dimethylformamide (250 mL) was treated
simultaneously with *t*-butyldiphenylsilyl chloride (94 g) and
imidazole (24 g) and stirring continued for 2 hours at room
temperature. The reaction mixture was treated with 1.0 M
10 hydrochloric acid (500 mL), and extracted with diethyl ether
(3 x 500 mL). The combined organic extracts were washed
successively with 1.0 M hydrochloric acid (500 mL),
saturated sodium hydrogen carbonate (500 mL), then dried and
concentrated *in vacuo*. The residue was purified by flash
15 chromatography eluting with mixtures of diethyl ether in
hexane (1:9 to 9:1 by volume) to give compound 2 as a clear
oil (67.6 g).

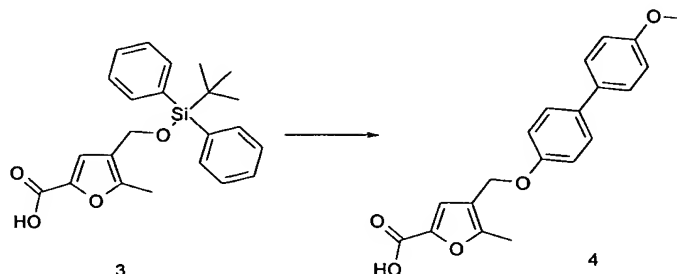
(b) 4-(*tert*-Butyl-diphenyl-silanyloxymethyl)-5-methyl-furan-
20 2-carboxylic acid (3)



A solution of 3-(*tert*-Butyl-diphenyl-silanyloxymethyl)-2-
methyl-furan (2) (30.0 g) in tetrahydrofuran (75 mL) was
cooled to -78°C with stirring and treated drop-wise with a
25 solution of *n*-butyllithium (2.5 M in hexanes, 71 mL) over 10

mins. The cooling bath was removed for 0.5 hours and then replaced. A large excess of solid carbon dioxide was added and the mixture allowed to warm to ambient temperature. The reaction mixture was acidified, with 1.0 M hydrochloric acid to pH 2 and extracted into diethyl ether (3 x 500 mL). The combined extracts were washed successively with 1.0 M hydrochloric acid (500 mL), water (500 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with mixtures of diethyl ether in pentane (1:5 to 5:1 by volume) to give compound **3** as a yellow oil (10.36 g). LC/MS System A: R_t = 4.33 mins, m/z (ES^-) = 393 (M^- for $C_{23}H_{26}O_4Si$).

(c) 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**)

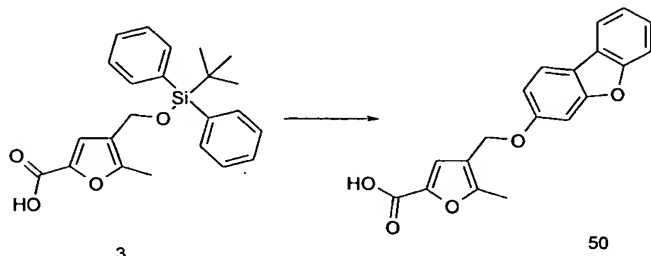


(i) 2-Chlorotrityl chloride resin (1g of nominal loading 1.3 mmol/g) was swelled with dichloromethane (20 mL). After draining, a solution of 4-(tert-butyl-diphenyl-silanyloxymethyl)-5-methyl-furan-2-carboxylic acid (**3**) (0.512 g) and diisopropylethylamine (0.91 mL) in dichloromethane (10 mL) was added and the mixture was shaken at ambient temperature for 16 hours. The resin was drained, washed sequentially with dichloromethane/triethylamine/methanol (20:1:3 by volume) (3 x 25 mL), dichloromethane (3 x 25 mL), *N,N*-dimethylformamide (2 x 25 mL), dichloromethane (6 x 25 mL), and diethyl ether (2 x 25 mL) and then dried at 40°C *in vacuo*.

(ii) The loaded resin from (i) (2.47 g) was swelled in tetrahydrofuran (15 mL), then treated tetrabutylammonium fluoride (12.8 mL of a 1 M solution in tetrahydrofuran) and shaken at room temperature for 16 hours. The resin was drained, washed sequentially with tetrahydrofuran/water (1:1 by volume), tetrahydrofuran, N,N-dimethylformamide, dichloromethane, diethyl ether, and then dried at 40°C *in vacuo*.

(iii) The loaded resin (2.83g) from (ii) was swelled in tetrahydrofuran (15 mL), and then treated with a solution of 4-hydroxy-4'-methoxydiphenyl (2.93 g) and triphenylphosphine (3.48 g) in tetrahydrofuran (20 mL), followed by the addition of diisopropylazodicarboxylate (2.96 g). The mixture was shaken at room temperature for 16 hours. The resin was drained, washed sequentially with tetrahydrofuran/water (1:1 by volume), tetrahydrofuran, N,N-dimethylformamide, dichloromethane, and then dried at 45°C *in vacuo*. The resin was treated with dichloromethane/trifluoroacetic acid (19:1 by volume) (20 mL) for 20 mins and the solution drained from the resin. This procedure was repeated. The combined solutions were concentrated *in vacuo* and the residue recrystallised from ethanol to afford compound **4** as a white solid (0.42 g). LC/MS System C: $R_t = 4.00$ mins, m/z (ES^-) = 337 (M^- for $C_{20}H_{18}O_5$).

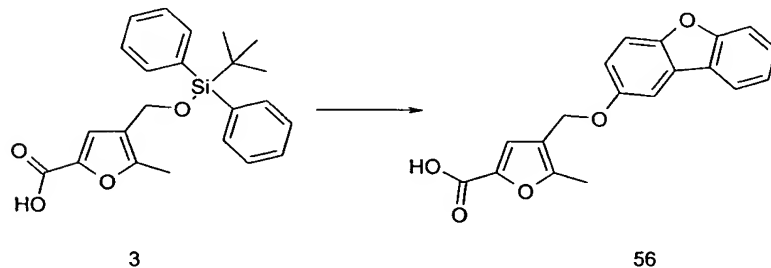
(d) 4-(Dibenzofuran-3-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**50**)



Compound (**50**) was prepared by adapting the procedure of
5 Example 1(c). LC/MS System B: $R_t = 1.79$ mins, m/z (ES^-) = 321
($(M-H)$ for $C_{19}H_{14}O_5$).

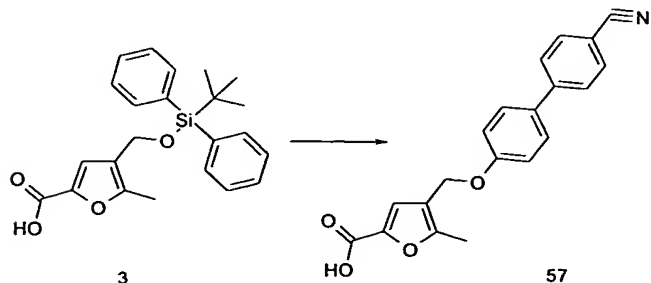
(e) 4-(Dibenzofuran-2-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**56**)

10



Compound (**56**) was prepared by adapting the procedure of
Example 1(c). LC/MS System B: $R_t = 1.76$ mins, m/z (ES^-) = 321
15 ($(M-H)$ for $C_{19}H_{14}O_5$).

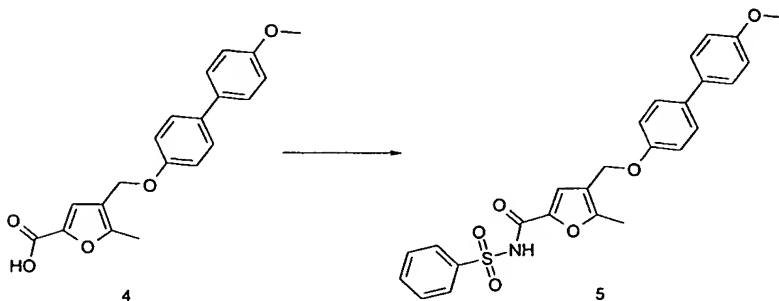
(f) 4-(4'-Cyano-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**57**)



Compound (57) was prepared by adapting the procedure of Example 1(c). LC/MS System B: $R_t = 1.72$ mins, m/z (ES^-) = 332 ($(M-H)$ for $C_{20}H_{15}NO_4$).

5

Example 2A: Synthesis of *N*-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (5)



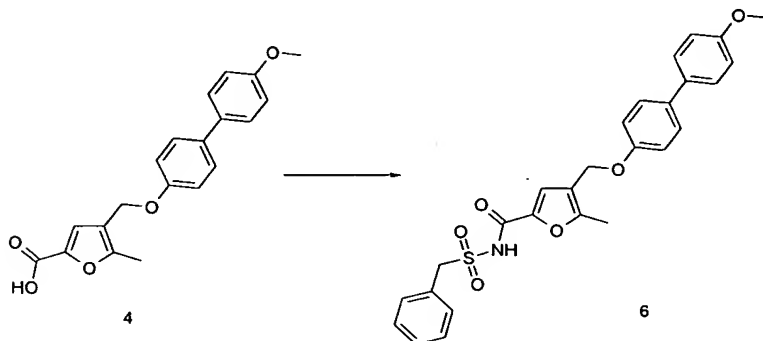
10

A stirred solution of 4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (4) (250 mg) in dichloromethane (50 mL) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (142 mg), 4-(*N,N*-dimethylamino)pyridine (2 mg) and benzenesulfonamide (232 mg). After 16 hours the reaction mixture was concentrated *in vacuo*, the residue dissolved in ethyl acetate (200 mL) and washed successively with water (20 mL), 1.0 M hydrochloric acid (20 mL), saturated sodium hydrogen carbonate solution (20 mL), brine (20 mL), dried and concentrated *in vacuo*. The crude product was purified by HPLC to afford compound 5 as a white solid (30 mg). LC/MS System D: $R_t = 5.45$ mins, m/z (ES^-) = 476 (M^- for $C_{26}H_{23}NO_6S$).

25

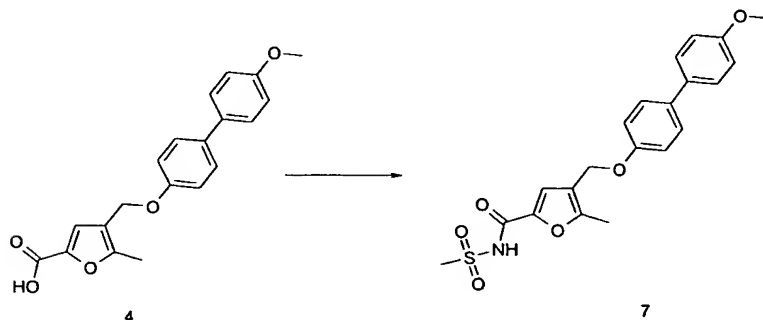
By adapting the procedure of Example 2A and using the appropriate sulphonamide there were prepared Examples 2B to 2G:

Example 2B: N-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-C-phenyl-methanesulfonamide (6)



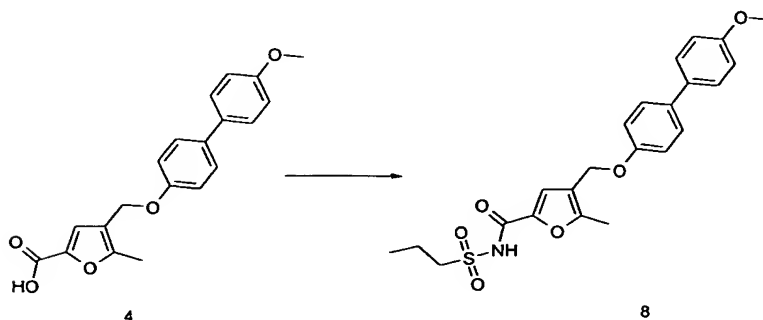
LC/MS System C: $R_t = 5.37$ mins, m/z (ES^-) = 490 (M^- for $C_{27}H_{25}NO_6S$).

Example 2C: N-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-methanesulfonamide (7)



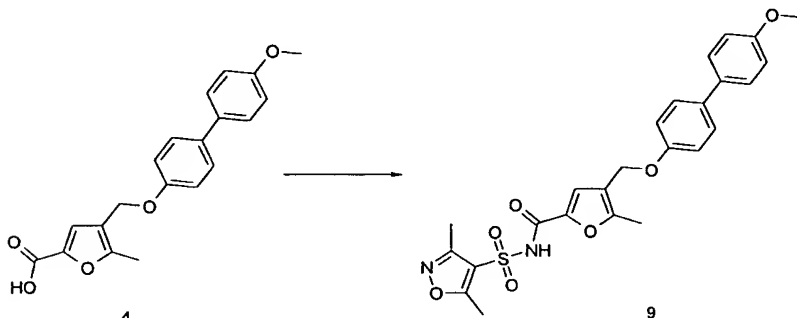
LC/MS System C: $R_t = 4.50$ mins, m/z (ES^-) = 414 (M^- for $C_{21}H_{21}NO_6S$).

Example 2D: Propane-1-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (8)



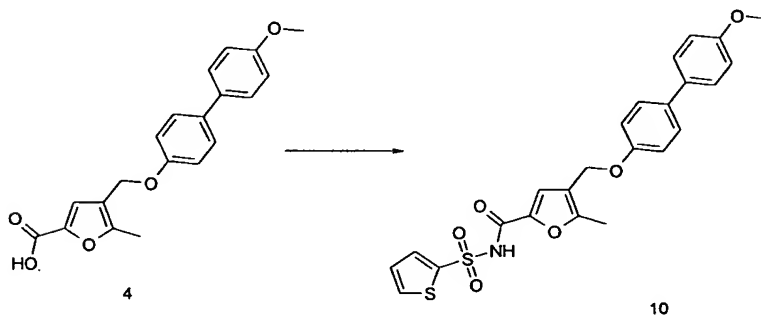
LC/MS System C: $R_t = 4.78$ mins, m/z (ES^-) = 442 (M^- for $C_{23}H_{25}NO_6S$).

Example 2E: 3,5-Dimethyl-isoxazole-4-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (9)



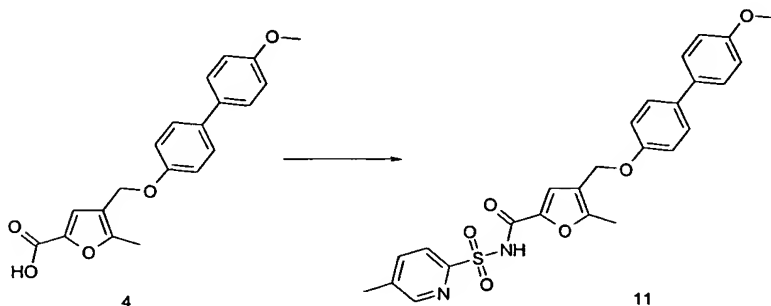
LC/MS System C: $R_t = 4.91$ mins, m/z (ES^-) = 495 (M^- for $C_{25}H_{24}N_2O_7S$).

Example 2F: Synthesis of Thiophene-2-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (10)



LC/MS System C: $R_t = 4.94$ mins, m/z (ES^-) = 482 (M^- for $C_{24}H_{21}NO_6S_2$).

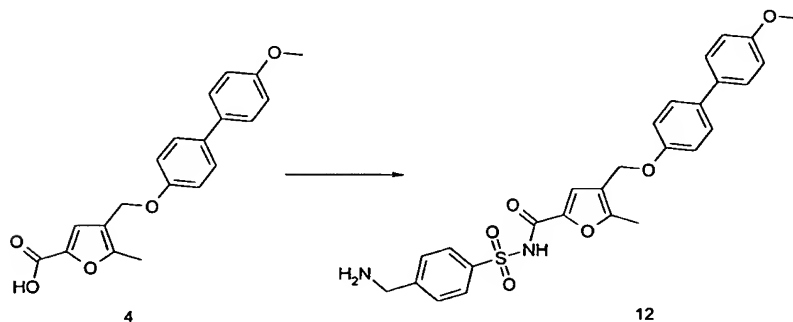
Example 2G: 5-Methyl-pyridyl-2-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (11)



5 LC/MS System D: $R_t = 10.09$ mins, m/z (ES^+) = 493 (MH^+ for $C_{26}H_{24}NO_6S$).

Example 2H: Synthesis of 4-Aminomethyl-N-[4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide trifluoroacetate (12)

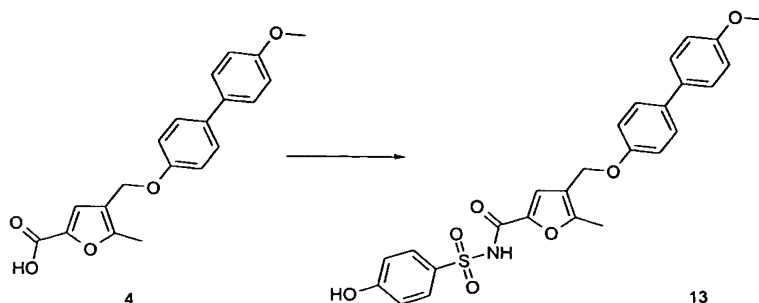
10



4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**) (50 mg) was reacted with (4-sulphamoyl-benzyl)-carbamic acid tert-butyl ester (85mg) in an analogous manner to that described in Example 2A. The intermediate tert-butyl carbamate was hydrolysed with 1% trifluoroacetic acid/dichloromethane over 24 hours, then concentrated *in vacuo* to give compound **12** as a white solid (10 mg). LC/MS System C: $R_t = 4.67$ mins, m/z (ES^-) = 493 (M^- for $C_{27}H_{26}N_2O_6S$).

20

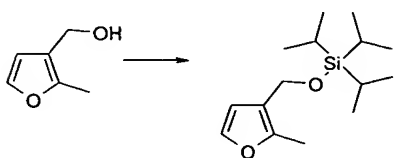
Example 2I: Synthesis of 4-Hydroxy-N-[4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (13)



5 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**) (50 mg) was reacted with acetic acid 4-sulphamoyl-phenyl ester (64 mg) in an analogous manner to that described in Example 2A. The acetic ester intermediate was hydrolysed with sodium methoxide (80 mg) in a mixture of
10 methanol (10mL) and water (1mL) for 1 hour. The solution was concentrated *in vacuo* then partitioned between dichloromethane (10 mL) and water (10 mL). The organic layer was washed with brine (10 mL), dried, filtered and concentrated *in vacuo*. The crude product was purified by
15 preparative HPLC (starting at 30% acetonitrile and increasing at a rate of 1% per minute up to 98% acetonitrile) to give compound **13** as a white solid (15 mg).
LC/MS System C: $R_t = 3.50$ mins, m/z (ES^-) = 492 (M^- for $C_{26}H_{23}N_2O_7S$).

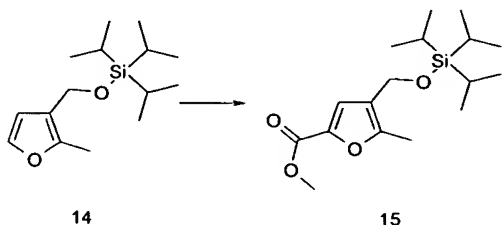
Example 3: Synthesis of 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (18)

(a) Triisopropyl-(2-methyl-furan-3-ylmethoxy)-silane (14)



Triisopropyl-(2-methyl-furan-3-ylmethoxy)-silane was prepared from (2-methyl-furan-3-yl)-methanol (**1**) (24.22 g) in an analogous manner to that described in Example 1 to give compound **14** as a clear oil (54.0 g).

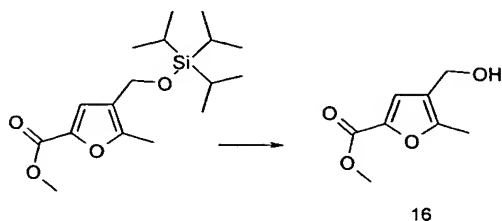
(b) 5-Methyl-4-triisopropylsilanyloxymethyl-furan-2-carboxylic acid methyl ester (15)



A solution of triisopropyl-(2-methyl-furan-3-ylmethoxy)-silane (**14**) (10.0 g) in tetrahydrofuran (300 mL) was cooled to -78°C with stirring was treated drop-wise with sec-butyl lithium (3.0 M in cyclohexane, 37 mL). After 1 hour the reaction mixture was treated drop-wise with a solution of methyl chloroformate (5.2 g) in tetrahydrofuran (30 mL) over 10 mins and stirring was continued at -78°C for 1 hour. The reaction mixture was then treated with saturated ammonium chloride solution (300 mL) and allowed to warm to ambient temperature. The two layers were separated and the organic phase washed with brine (300 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with ethyl acetate/pentane (1:9 by volume) to give

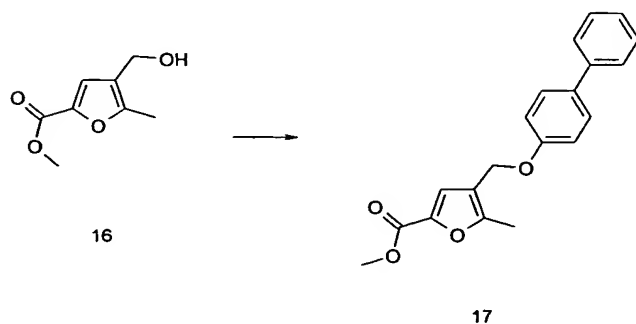
compound **15** as a clear oil.

(c) 4-Hydroxymethyl-5-methyl-furan-2-carboxylic acid methyl ester (**16**)



A stirred solution of 5-methyl-4-triisopropylsilyloxymethyl-furan-2-carboxylic acid methyl ester (**15**) (5.2 g) in tetrahydrofuran (200 mL) was treated with tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran, 3.2 mL) and stirring continued for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue taken up in ethyl acetate (350 mL) and washed with water (150 mL). The aqueous phase was re-extracted with ethyl acetate (2 x 100 mL). The combined extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography eluting with ethyl acetate/pentane (1:1 by volume) to give compound **16** as a yellow oil.

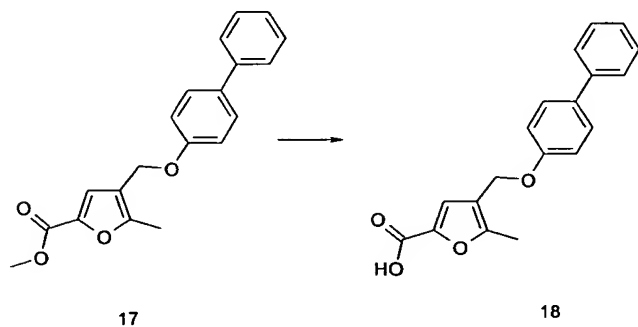
(d) 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**17**)



A solution of 4-hydroxymethyl-5-methyl-furan-2-carboxylic acid methyl ester (**16**) (1g) in anhydrous tetrahydrofuran

(20mL) was cooled to 0°C under a nitrogen atmosphere. 4-Hydroxybiphenyl (3g) and triphenylphosphine (4.61g) were added and the mixture was treated with di-isopropylazodicarboxylate (3.46mL) dropwise. The mixture was
5 stirred at 0°C for 10min then cooling was removed and the mixture stirred for a further 3 hours. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate (50mL) and water (100mL). The organic phase was separated, dried and evaporated. The residue was
10 purified by flash chromatography, eluting with pentane /ethyl acetate 9:1 by volume to give a mixture of the title compound and 4-hydroxybiphenyl (1.8g). This material was purified further by flash chromatography eluting with dichloromethane/methanol 99:1 by volume to give compound **17**
15 as a white solid (200mg). LCMS System A: $R_t = 4.2$ mins.

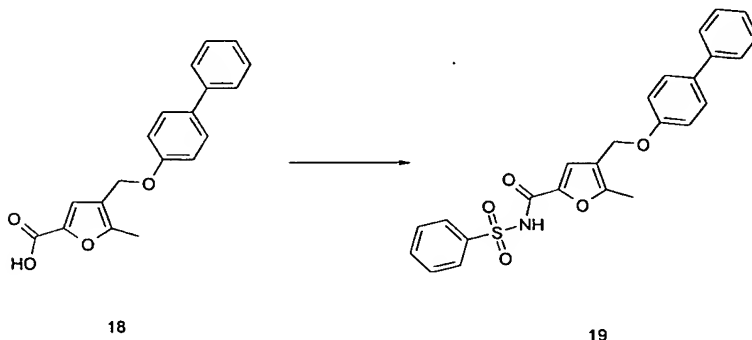
(e) 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**18**)



20 1M Aqueous lithium hydroxide (18mL) was added to solution of 4-(biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**17**) (1g) in tetrahydrofuran/methanol (2:1 by volume, 100mL) and the mixture stirred at room temperature for 5h. The solvent was removed in vacuo, the residue
25 dissolved in water (20mL) and the solution acidified to pH6 with aqueous dilute hydrochloric acid. The mixture was evaporated to dryness and the residue was purified by HPLC

to afford compound **18** as a white solid (210mg). LC/MS System B: $R_t = 4.80$ mins, $m/z = 307$ ((M-1) for $C_{19}H_{16}O_4$).

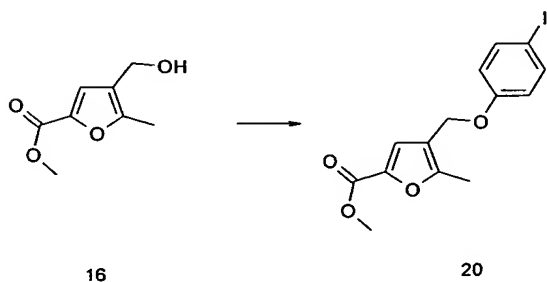
Example 4: Synthesis of N-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (19)



Compound (**19**) was prepared by adapting the procedure of Example 2A. LC/MS System D: $R_t = 9.18$ mins, m/z (ES^-) = 446 (M^- for $C_{25}H_{21}NO_5S$).

Example 5: Synthesis of 4-(4'-Acetyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (21)

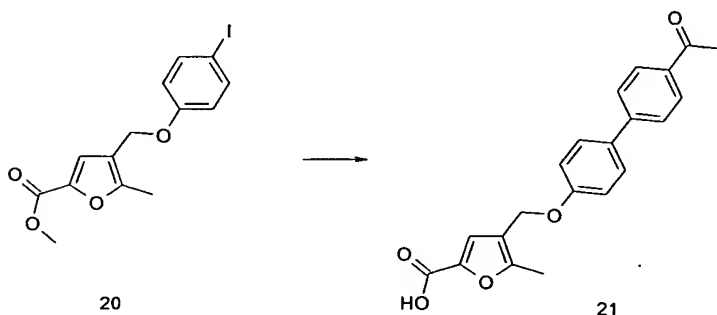
(a) 4-(4-Iodo-phenoxy-methyl)-5-methyl-furan-2-carboxylic acid methyl ester (**20**)



A solution of 4-hydroxymethyl-5-methyl-furan-2-carboxylic acid methyl ester (**16**) (1.14 g) in tetrahydrofuran (15 mL) was cooled to 0°C with stirring and treated with 4-iodophenol (4.6 g), triphenylphosphine (5.5 g) and diisopropylazodicarboxylate (4.2 g). After 10 minutes the cooling bath was removed. After 3 hours the reaction mixture

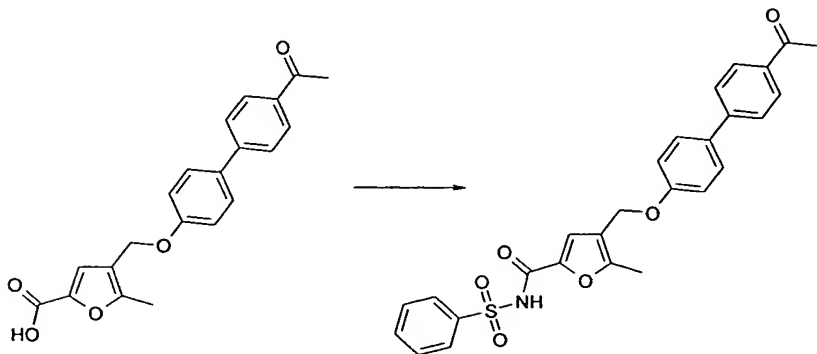
was concentrated *in vacuo* and taken up in ethyl acetate (100 mL) and washed successively with water (100 mL), 1.0 M aqueous sodium hydroxide solution (100 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with ethyl acetate/hexane (1:4 by volume) to give compound **20** as a white solid (1.58 g).

(b) 4-(4'-Acetyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**21**)



A stirred mixture of 4-(4-iodo-phenoxy-methyl)-5-methyl-furan-2-carboxylic acid methyl ester (**20**) (0.26 g), 4-acetylphenylboronic acid (0.15 g), N,N-dimethylformamide (30 mL), potassium acetate (0.26 g) and [1,1'-bis(diphenylphosphino) ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (40 mg) was heated at 90°C over night. The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (30 mL) and washed successively with water (30 mL), brine (30 mL), dried and concentrated *in vacuo*. The residue was dissolved in a mixture of tetrahydrofuran/methanol (2:1 by volume) (30 mL) and 1.0 M aqueous lithium hydroxide solution (6.78 mL) and stirred for 16 hours. The reaction mixture was acidified to pH 2 using 0.1 M hydrochloric acid and extracted with ethyl acetate (3 x 25 mL). The extract was dried, concentrated *in vacuo* and the residue purified by HPLC to give compound **21** as a white solid (50mg). LC/MS System C: R_t = 4.18 mins, m/z (ES^-) = 349 (M^- for $C_{21}H_{18}O_5$).

Example 6: Synthesis of *N*-[4-(4'-Acetyl-biphenyl-4-ylloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (22)



5

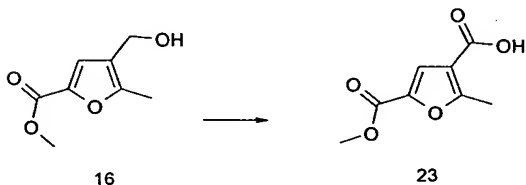
21

22

Compound (22) was prepared by adapting the procedure of Example 2A. LC/MS System D: $R_t = 9.87$ mins, m/z (ES^+) = 490 (MH^+ for $C_{27}H_{23}NO_6S$).

10 **Example 7: Synthesis of 4-(4'-Methoxy-biphenyl-4-ylcarbonyl)-5-methyl-furan-2-carboxylic acid (24)**

(a) 5-methyl-furan-2,4-dicarboxylic acid-2-methyl ester (23)



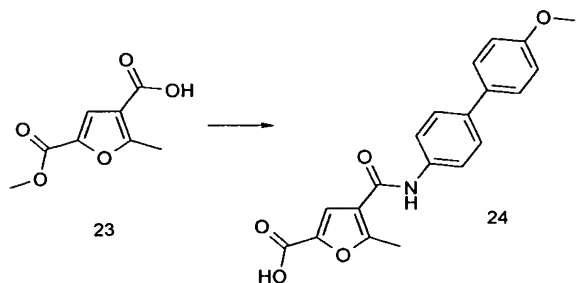
16

23

15 Jones' reagent (Prepared according to Fieser and Fieser, Reagents for Organic Synthesis, Volume 1, page 142, 1967) was added drop-wise to a stirred solution of 4-hydroxymethyl-5-methyl-furan-2-carboxylic acid methyl ester (16) (100 mg) in acetone (10 mL) until the orange
20 colouration just remained. Stirring was continued for a further 5 hours then the reaction mixture was diluted with diethyl ether (20 mL) and filtered. The filtrate was dried

and concentrated *in vacuo* to afford compound **23** as a buff coloured solid.

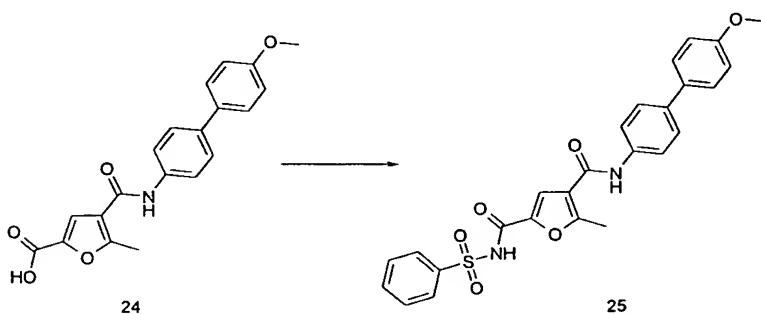
(b) 4-(4'-Methoxy-biphenyl-4-ylcarbamoyl)-5-methyl-furan-2-carboxylic acid (**24**)



To a solution of 5-methyl-furan-2,4-dicarboxylic acid-2-methyl ester (**23**) (100 mg) in N,N-dimethylformamide (3.0 mL) was added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (228 mg), diisopropylethylamine (0.56 mL) and 4'-methoxy-biphenyl-4-ylamine (120 mg). The resulting solution was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate (20 mL) and washed successively with water (2 x 20 mL), 0.1 M hydrochloric acid (20 mL), water (20 mL), saturated sodium hydrogen carbonate (10 mL) and brine (10 mL). This solution was dried and concentrated *in vacuo*. The residue (170 mg) was dissolved in dichloromethane (5 mL), treated with triethylamine (0.3 mL) and a scavenger resin PS-TsCl (0.6 g) and the mixture shaken for 3 hours at room temperature. The reaction mixture was filtered and concentrated *in-vacuo*. The residue was dissolved in methanol/tetrahydrofuran (1:3 by volume) (20 mL), treated with 1.0 M aqueous lithium hydroxide solution (2.0 mL) and allowed to stir at room temperature for 4 hours. The pH of the reaction mixture was adjusted to between pH 4 and pH 5 by careful addition of 1.0 M hydrochloric acid (1.0 mL) and partly concentrated *in vacuo*.

The residue was then partitioned between ethyl acetate (2 x 25 mL) and water (25 mL) and the combined organic extracts were washed with brine (35 mL), dried (Na₂SO₄), and concentrated *in vacuo* afforded compound **24** as beige solid (58 mg). LC/MS System D: R_t = 7.23 mins, m/z (ES⁺) = 351 (MH⁺ for C₂₀H₁₇NO₅).

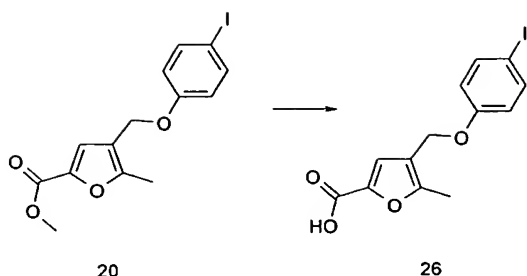
Example 8: Synthesis of 5-Benzenesulfonylamino-carbonyl-2-methyl-furan-3-carboxylic acid (4'-methoxy-biphenyl-4-yl)-amide (25)



Compound **25** was synthesised from 4-(4'-Methoxy-biphenyl-4-ylcarbamoyl)-5-methyl-furan-2-carboxylic acid (**24**) (35 mg) in an analogous manner to that described in Example 2A to give the title compound as a white solid (7 mg). LC/MS System A: R_t = 3.86mins, m/z (ES-) = 489 (M-1 for C₂₆H₂₂N₂O₆S).

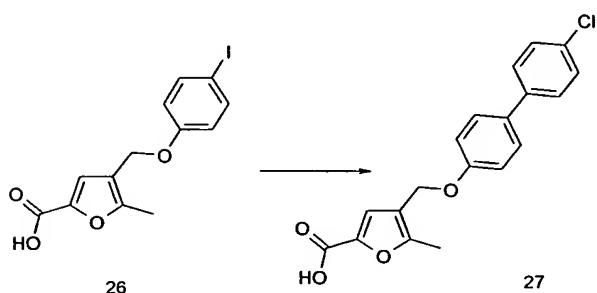
Example 9: Synthesis of 4-(4'-Chloro-biphenyl-4-ylloxymethyl)-5-methyl-furan-2-carboxylic acid (27) and 4-(4-Benzo[1,3]dioxol-5-yl-phenoxy-methyl)-5-methyl-furan-2-carboxylic acid (28)

(a) 4-(4-Iodo-phenoxy-methyl)-5-methyl-furan-2-carboxylic acid (**26**)



A stirred solution of 4-(4-iodo-phenoxy)-5-methyl-furan-2-carboxylic acid methyl ester (**20**) (2.7 g) in tetrahydrofuran (25 mL) was treated with a solution of lithium hydroxide (1.5 g) in water (2 mL). After 3 hours the reaction mixture was diluted with water and acidified to pH 2 with 1.0 M hydrochloric acid. The white precipitate was filtered off and dried *in vacuo*. The solid was triturated with ethyl acetate at 0°C then collected by filtration to give compound **26** as a white solid (1.83 g). LC/MS system A: $R_t = 1.74$ min.

(b) 4-(4'-Chloro-biphenyl-4-yloxy)-5-methyl-furan-2-carboxylic acid (**27**)



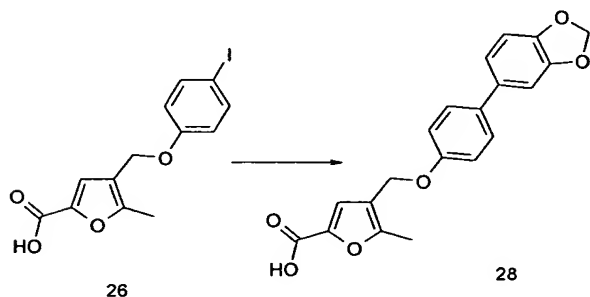
(i) 2-Chlorotriethyl chloride resin (2.55 g of nominal loading 1.3 mmol/g) was swelled with dichloromethane (20 mL). After draining, a solution of 4-(4-iodo-phenoxy)-5-methyl-furan-2-carboxylic acid (**26**) (1.18 g) and diisopropylethylamine (2.3 mL) in dichloromethane (30 mL) was added and the mixture was shaken at room temperature for 72 hours. The resin was drained, washed sequentially with dichloromethane/triethylamine/methanol (20:1:3 by volume) (3

x 30 mL), dichloromethane (6 x 30 mL), N,N-dimethylformamide (2 x 25 mL), dichloromethane (6 x 25 mL), and diethyl ether (2 x 25 mL) and dried at 40°C *in vacuo*.

- 5 (ii) A stirred mixture of the resin from (i) (0.38g), 4-chlorophenylboronic acid (0.30 g), [1,1'-bis-(diphenylphosphino)-ferrocene]-dichloropalladium(II) complex with dichloromethane (1:1) (30 mg), potassium acetate (0.20 g) in N,N-dimethylformamide (15 mL) was heated at 40°C for
10 48 hours. The resin was drained, then washed sequentially with tetrahydrofuran/water (1:1 by volume), tetrahydrofuran, N,N-dimethylformamide, dichloromethane, diethyl ether and then dried at 45°C *in vacuo*. The resin was treated with dichloromethane/trifluoroacetic acid (19:1 by volume) (20
15 mL) for 20 mins and the solution drained from the resin. This procedure was repeated. The combined solutions were concentrated *in vacuo* and the residue purified by HPLC to afford compound **27** as a white solid (43 mg). LC/MS System D: R_t = 8.83 mins, m/z (ES^-) = 341 (M^- for $C_{19}H_{15}ClO_4$).

20

(c) 4-(4-Benzo[1,3]dioxol-5-yl-phenoxyethyl)-5-methyl-furan-2-carboxylic acid (**28**)



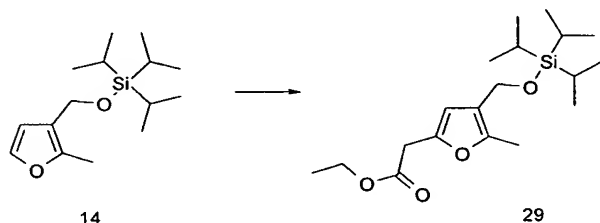
Compound **28** was synthesised from the resin from (i) in step (b) above and 3,4-methylenedioxyphenylboronic acid in an analogous manner to that described in step (ii) above. LC/MS System C: $R_t = 4.60$ mins, m/z (ES^-) = 351 (M^- for $C_{20}H_{16}O_6$).

5

Example 10: Synthesis of [4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acetic acid (31) and 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acetic acid (32)

10

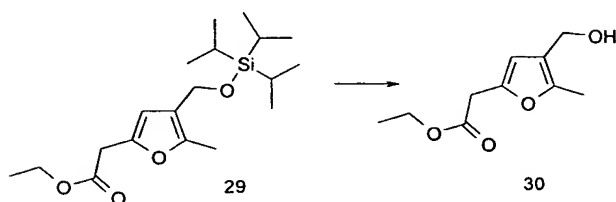
(a) (5-Methyl-4-triisopropylsilanyloxymethyl-furan-2-yl)-acetic acid ethyl ester (**29**)



A solution of triisopropyl-(2-methyl-furan-3-ylmethoxy)-silane (**14**) (5.0 g) in tetrahydrofuran (15 mL) was cooled to -78°C with stirring. This solution was treated drop-wise with n-butyl lithium (2.5 M in hexanes, 8.94 mL). The resulting solution was warmed to 0°C and allowed to stand for 30 minutes after which a solution of dried zinc chloride (3.04 g) in tetrahydrofuran (10 mL) was added and the resulting solution allowed to stand for a further 1 hour at room temperature. Concurrently, a second reaction vessel was charged with tetrahydrofuran (10 mL), nickel(II) acetylacetonate (120 mg), and triphenylphosphine (122 mg) and cooled (-5°C). Ethyl bromoacetate (1.03 mL) was added to this mixture, followed by the addition of the previously prepared solution of the furyl-zinc chloride. The resulting reaction mixture was allowed to warm to room temperature then stirred for a further 16 hours at room temperature. The

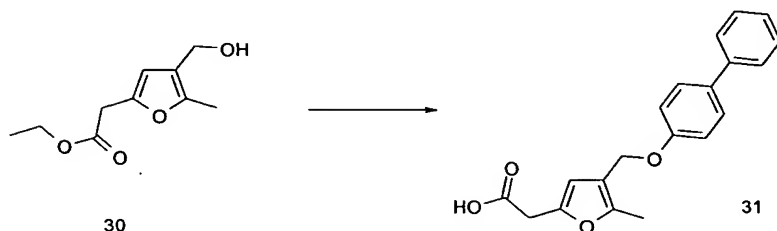
reaction was quenched by the addition of saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were successively washed with water (200 mL) and brine (250 mL), dried, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography using a gradient elution (diethyl ether /petroleum ether (40-60°) 1:49 to 1:25 by volume) to give compound 29 as a clear oil (1.44 g). LC/MS System A: $R_t = 5.16\text{min}$.

(b) (4-Hydroxymethyl-5-methyl-furan-2-yl)-acetic acid ethyl ester (**30**)



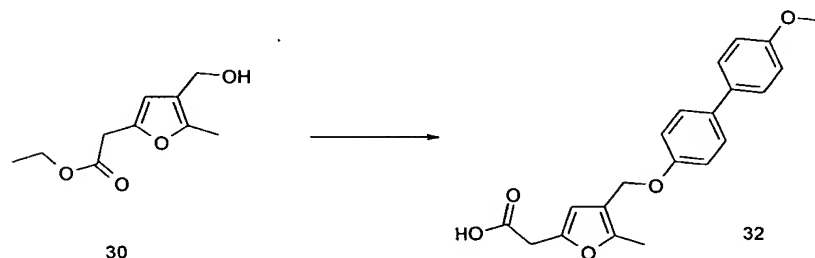
A solution of (5-methyl-4-triisopropylsilyloxymethyl-furan-2-yl)-acetic acid ethyl ester (**29**) (0.5 g) in tetrahydrofuran (3.0 mL) was cooled to 0°C with stirring and treated with tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran, 2.82 mL) under argon. After 30 minutes, the resulting solution was concentrated *in-vacuo* and partitioned between water (30 mL) and ethyl acetate (4 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with diethyl ether/petroleum ether (1:1 by volume) to give compound **30** as a clear oil (188 mg). LC/MS System A: $R_t = 2.34\text{ mins}$.

(c) [4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acetic acid (31)



Compound (31) was prepared from compound (30) in an
5 analogous manner to the methods described in Examples 3(d)
and 3(e). LC/MS System C: $R_t = 4.97$ mins, m/z (ES^-) = 321 (M^-
for $C_{20}H_{18}O_4$).

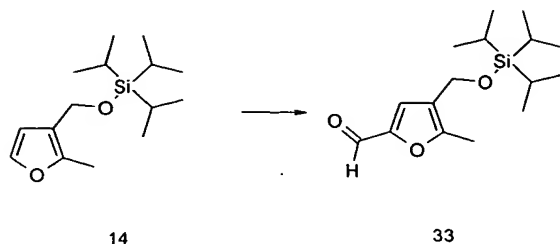
(d) [4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acetic acid (32)



Compound (32) was prepared from compound (30) in an
analogous manner to the methods described in Examples 3(d)
and 3(e). LC/MS System C: $R_t = 4.94$ mins, m/z (ES^-) = 351 (M^-
15 for $C_{21}H_{20}O_5$).

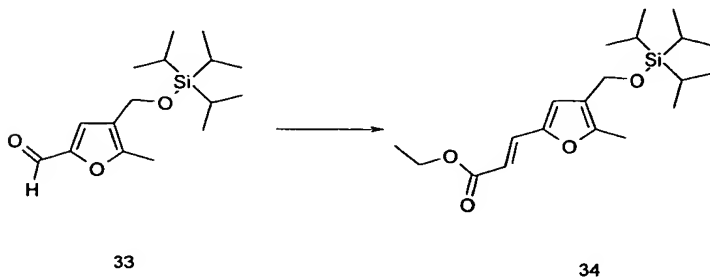
Example 11: Synthesis of 3-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionic acid (37) and N-{3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionyl}-
20 **benzene sulfonamide (38)**

(a) 5-Methyl-4-triisopropylsilanyloxymethyl-furan-2-carbaldehyde (**33**)



A solution of triisopropyl-(2-methyl-furan-3-ylmethoxy)-silane (**14**) (10 g) in tetrahydrofuran (250 mL) was cooled to -78°C with stirring, and then sec-butyllithium (1.3 M in cyclohexane; 37.25 mL) was added drop-wise over 10 mins. After stirring for 45 mins at -78°C, the cooling bath was removed for a period of 15 mins then re-introduced. A solution of N,N-dimethylformamide (14.4 mL) in tetrahydrofuran (25 mL) was added drop-wise and the resulting reaction mixture was stirred at -78°C for a further 2 hours. The reaction mixture was allowed to warm to room temperature and then poured into saturated ammonium chloride solution (150 mL). This mixture was extracted with diethyl ether (2 x 350 mL), and the combined organic extracts were washed with water (500 mL) and brine (500 mL), dried, and concentrated *in vacuo* to give compound **33** as an amber coloured oil. LC/MS System A: R_t = 4.86 mins.

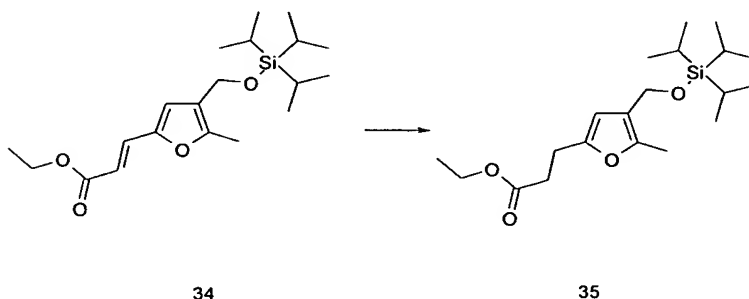
(b) 3-(5-Methyl-4-triisopropylsilanyloxymethyl-furan-2-yl)-acrylic acid ethyl ester (**34**)



A stirred solution of 5-methyl-4-

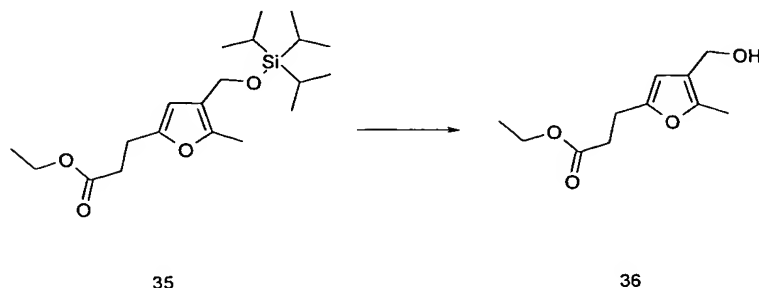
triisopropylsilanyloxymethyl-furan-2-carbaldehyde (**33**) (10.6 g) in tetrahydrofuran (25 mL) was treated with triethylphosphonoacetate (7.81 mL) and lithium hydroxide (1.65 g). The resulting mixture was stirred for 16 hours then concentrated *in vacuo* and the residue partitioned between water (100 mL) and diethyl ether (3 x 100 mL). The combined organic extracts were further washed with water (200 mL) and brine (200 mL), then dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with diethyl ether/petroleum ether (1:40 by volume) to give compound **34** as a clear yellow oil (10.56 g). LC/MS System A: R_t = 4.59 mins.

(c) 3-(5-Methyl-4-triisopropylsilanyloxymethyl-furan-2-yl)-propionic acid ethyl ester (**35**)



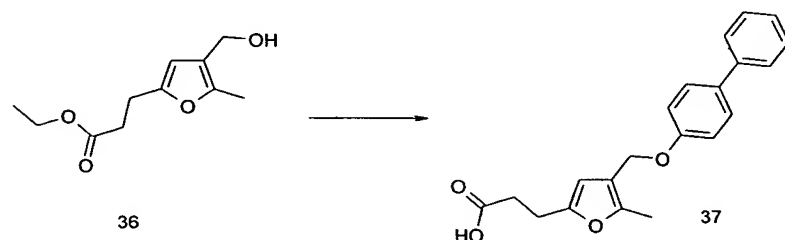
A solution of 3-(5-methyl-4-triisopropylsilanyloxymethyl-furan-2-yl)-acrylic acid ethyl ester (**34**) (1.0 g) in ethyl acetate (70 mL) was treated with 5% w/w palladium on carbon (350 mg) and hydrogenated at 1 atmosphere for exactly 1½ hours at room temperature. The reaction mixture was filtered through filter-aid and then concentrated *in vacuo* to afford compound **35** as a clear oil (1.05 g). LC/MS System A: R_t = 5.52 mins.

(d) 3-(4-Hydroxymethyl-5-methyl-furan-2-yl)-propionic acid ethyl ester (**36**)



Compound (**36**) was prepared in the form of a clear oil from
5 compound (**35**) by adapting the procedure described in Example
3(c). LC/MS System A: R_t = 2.68 mins.

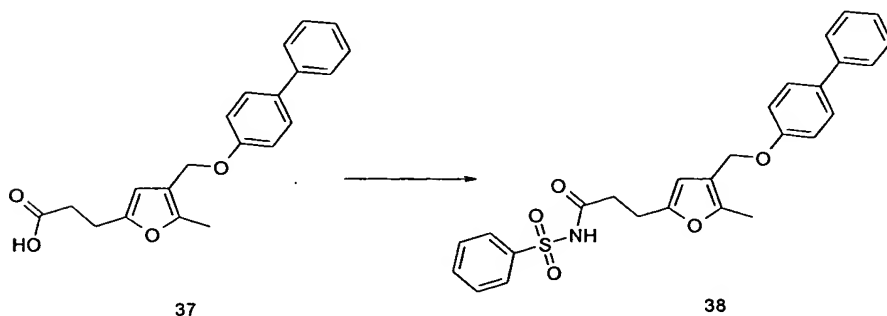
(e) 3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-
propionic acid (**37**)



To a stirred, cooled 0°C solution, in tetrahydrofuran (2.5
mL), a solution of 3-(4-hydroxymethyl-5-methyl-furan-2-yl)-
propionic acid ethyl ester (**36**) (400 mg) in tetrahydrofuran
(2.5 mL) was cooled to 0°C and treated successively with
15 triphenylphosphine (542 mg), biphenyl-4-ol (353 mg) and
diisopropylazodicarboxylate (0.41 mL). After stirring for 10
mins at 0°C the reaction mixture was allowed to warm to room
temperature and then stirred for a further 16 hours. The
reaction mixture was concentrated *in-vacuo* then re-dissolved
20 in dichloromethane (15 mL) and treated with triethylamine
(1.50 mL) and a scavenger resin PS-TsCl (2.5 g) and the
mixture was shaken for 6 hours at room temperature. The
reaction mixture was purified by flash chromatography,

eluting with a mixture of diethyl ether in petroleum ether (40-60°C) (7:93 by volume). The purified product (320 mg) was dissolved in methanol/tetrahydrofuran (2:1 by volume) (18 mL), treated with 1.0 M aqueous lithium hydroxide solution (9 mL) and allowed to stir at room temperature for 6 hours. The pH of the reaction mixture was adjusted to between pH4 and pH5 by the addition of 1.0 M hydrochloric acid (~ 5.0 mL), then treated with saturated ammonium chloride (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were further washed with brine (35 mL), then dried (sodium sulphate) and concentrated *in vacuo*. A sample of the crude product (50 mg) was purified by HPLC to give compound **37** as white solid (25mg). LC/MS System C: $R_t = 5.33$ mins, m/z (ES^-) = 335 (M^- for $C_{21}H_{20}O_4$).

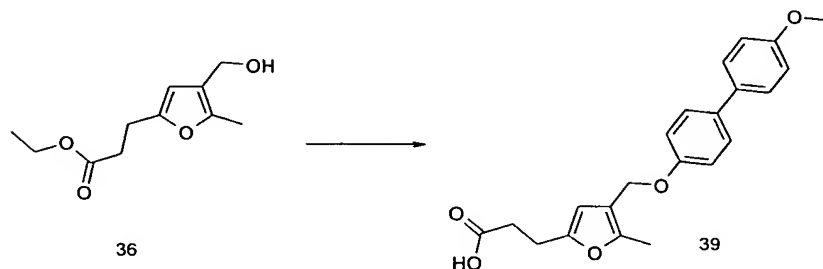
(f) *N*-{3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionyl}-benzene sulfonamide (**38**)



Compound (**38**) was prepared from compound (**37**) by the procedure of Example 2A. LC/MS System C: $R_t = 5.82$ mins, m/z (ES^-) = 475 (M^- for $C_{27}H_{25}O_5S$).

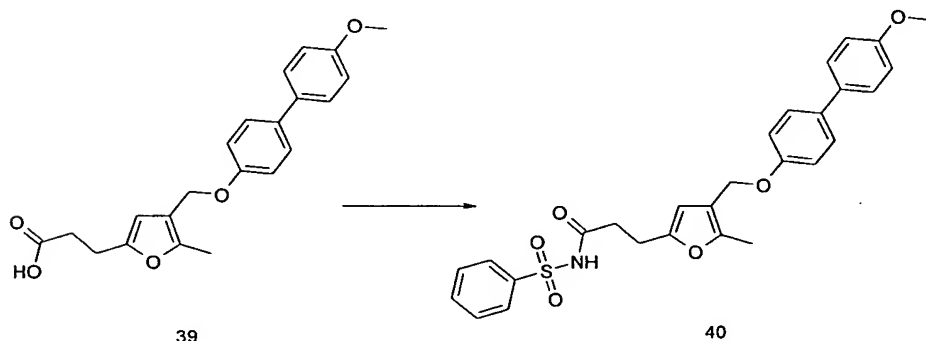
Example 12: Synthesis of 3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionic acid (39**) and *N*-{3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionyl}-benzene sulfonamide (**40**)**

(a) 3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionic acid (**39**)



Compound (**39**) was prepared from compound (**36**) in an analogous manner to that described in Example 11(e). LC/MS System C: $R_t = 5.31$ mins, m/z (ES^-) = 365 (M^- for $C_{22}H_{22}O_5$).

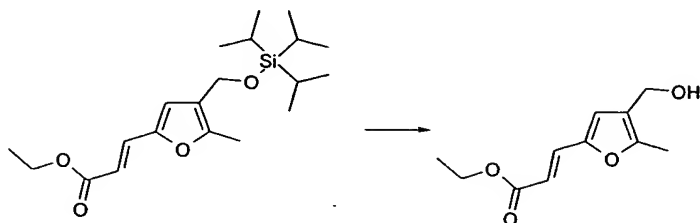
(b) N-{3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionyl}-benzene sulfonamide (**40**)



Compound (**40**) was prepared from compound (**39**) by the procedure of Example 2A. LC/MS System C: $R_t = 5.78$ mins, m/z (ES^-) = 504 (M^- for $C_{28}H_{27}NO_6S$).

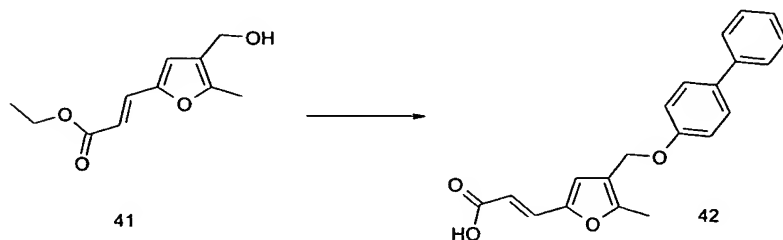
Example 13: Synthesis of 3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acrylic acid (42**) and 3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acrylic acid (**43**)**

(a) 3-(4-Hydroxymethyl-5-methyl-furan-2-yl)-acrylic acid ethyl ester (**41**)



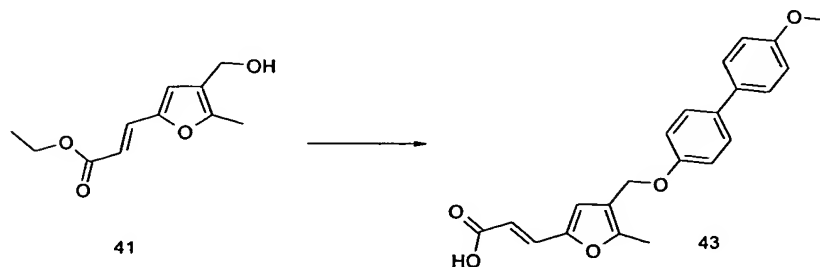
Compound (**41**) was prepared in the form of a yellow oil from
 5 compound (**34**) by adapting the procedure described in Example
 3(c). LC/MS System A: $R_t = 2.82$ mins.

(b) 3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-
 acrylic acid (**42**)



Compound (**42**) was prepared from compound (**41**) by adapting
 the procedure of Example 11(e). LC/MS System C: $R_t = 4.91$
 mins, m/z (ES^-) = 333 (M^- for $C_{21}H_{18}O_4$).

(c) 3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-
 2-yl]-acrylic acid (**43**)



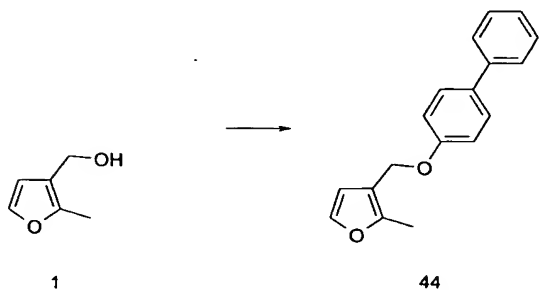
Compound (**43**) was prepared from compound (**41**) by adapting
 the procedure of Example 11(e). LC/MS System C: $R_t = 4.85$

mins, m/z (ES^-) = 363 (M^- for $C_{22}H_{20}O_5$).

Example 14A: Synthesis of 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid benzoylamide (46)

5

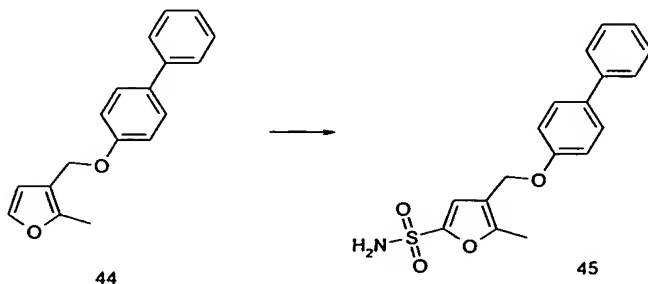
(a) 3-(Biphenyl-4-yloxymethyl)-2-methyl-furan (44)



A solution of (2-methyl-furan-3-yl)-methanol (**1**) (5.0 g) in diethyl ether (75 mL) was cooled to 0°C with stirring and
10 treated with triphenylphosphine (12.85 g) and biphenyl-4-ol (7.59 g). The resulting solution was then treated drop-wise with diisopropylazodicarboxylate (9.75 mL). After stirring for 10 minutes at 0°C the reaction mixture was allowed to warm to room temperature and then stirred for a further 3
15 hours. The reaction mixture was then filtered and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with diethyl ether/petroleum ether (1:19 by volume), to give compound **44** as a white solid (7.0 g). LC/MS System A: R_t = 4.38 mins.

20

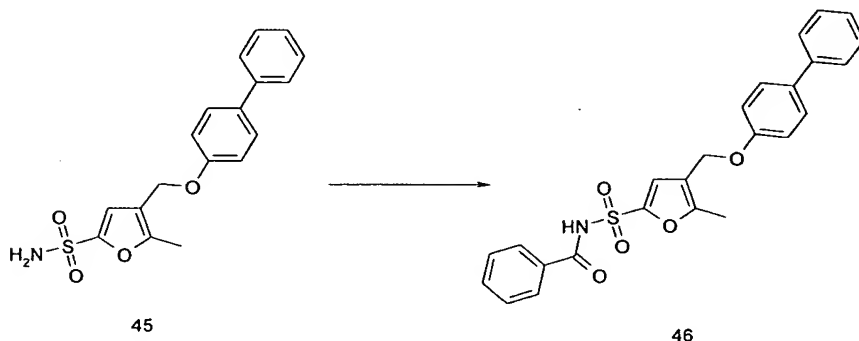
(b) 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid amide (45)



A solution of 3-(biphenyl-4-yloxymethyl)-2-methyl-furan (**44**) (5g) in tetrahydrofuran (30 mL) was cooled to -78°C with stirring and was treated with butyllithium (2.5 M in hexanes; 9.84 mL) drop-wise over 10 minutes. After stirring
5 for 45 mins at -78°C, cooling was removed for a period of 15 minutes then re-introduced. A stream of sulphur dioxide gas was then passed over the surface of the reaction mixture until the pH of the reaction was between pH6 and pH7.

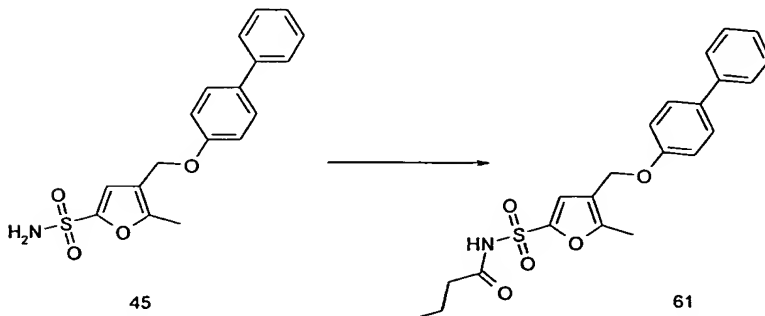
Stirring was continued for a further 1.5 hours at -78°C and
10 then pentane was added (50 mL). The resulting precipitate was collected by filtration and then re-suspended in water (75 mL). This suspension was cooled to 0°C and treated with sodium acetate (3.88 g) and hydroxylamine-O-sulfonic acid (2.67 g) and stirred at room temperature for 16 hours. The
15 reaction mixture was diluted with water (300 mL) and extracted into ethyl acetate (3 x 250 mL). The combined organic extracts were washed successively with saturated sodium hydrogen carbonate (300 mL) and brine (300 mL), dried, and concentrated *in vacuo*. This material was purified
20 by flash chromatography, eluting with diethyl ether/petroleum ether (2:3 by volume) to give a beige coloured solid (998 mg). A sample of this material (100 mg) was further purified by HPLC to give compound **45** as white solid (55 mg). LC/MS System A: $R_t = 3.70$ mins.

(c) 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid benzoylamide (**46**)



To a stirred solution of benzoic acid (61 mg) in a mixture
5 of tetrahydrofuran (10 mL) and N,N-dimethylformamide (5 mL)
was added 4-(N,N-dimethylamino)pyridine (3.0 mg), 1-(3-
dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (118
mg) and 4-(biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic
acid amide (**45**) (206 mg). After 16 hours at room temperature
10 the reaction mixture was concentrated *in-vacuo*, then
partitioned between 0.1 M hydrochloric acid (30 mL) and
ethyl acetate (3 x 30 mL). The combined organic extracts
were washed with brine (25 mL), dried (MgSO₄) and
concentrated *in vacuo*. The crude product was purified by
15 HPLC to give compound **46** as light beige solid (17 mg). LC/MS
System C: R_t = 5.69 mins, m/z (ES⁻) = 446 (M⁻ for C₂₅H₂₁NO₅S).

Example 14B: Synthesis of 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulphonic acid butyryl-amide (61**)**



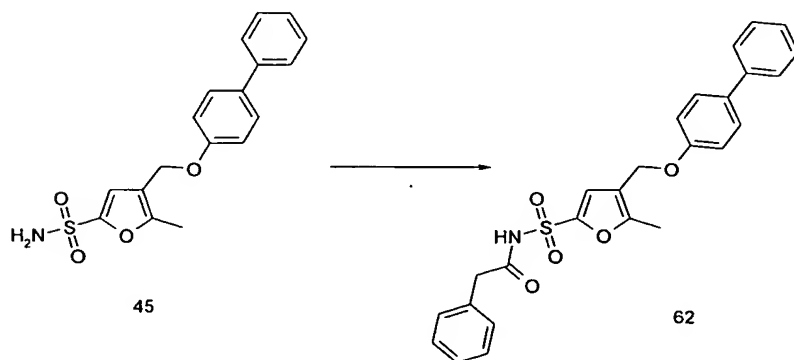
To a stirred solution of 4-(biphenyl-4-yloxymethyl)-5-

methyl-furan-2-sulphonic acid amide (**45**) (50mg, 0.146mmoles) in dichloromethane (5.0ml) was added triethylamine (26µl, 0.189mmoles), dimethyl-pyridin-4-yl-amine (1mg) and butyryl chloride (19µl, 0.184mmoles). After stirring for 16 hours at room temperature the reaction mixture was concentrated *in vacuo*, and the residue was purified by HPLC to give compound **61** as an off-white solid (48mg). LC/MS System C: $R_t = 3.82$ mins, m/z (ES^-) = 412 ((M-H) for $C_{22}H_{23}NO_5S$).

10

By adapting the procedure of Example 14B there were prepared Examples 14C to 14E :

Example 14C: 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulphonic acid phenylacetyl-amide (62)

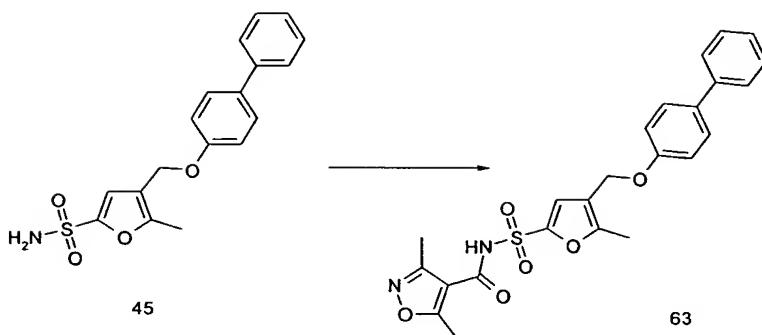


15

LC/MS System C: $R_t = 4.20$ mins, m/z (ES^-) = 460 ((M-H) for $C_{26}H_{23}NO_5S$).

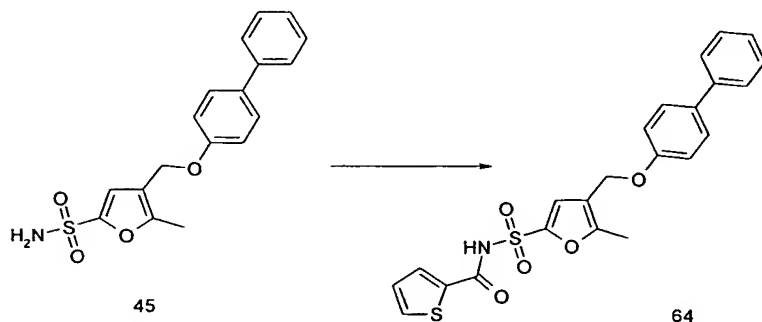
Example 14D: 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulphonic acid (3,5-dimethyl-isoxazole-4-carbonyl)-amide (63)

20



LC/MS System C: $R_t = 3.98\text{mins}$, m/z (ES^-) = 465 ((M-H) for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_6\text{S}$).

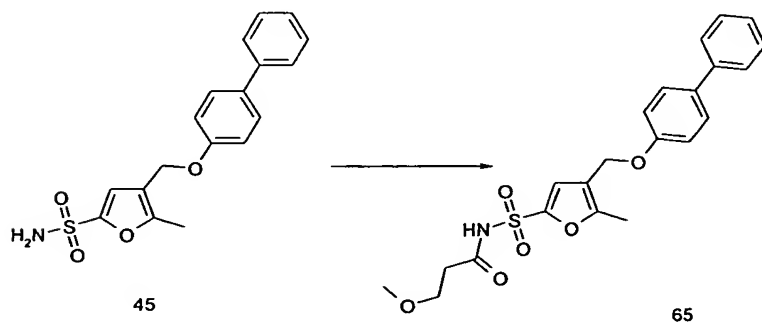
5 **Example 14E: 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulphonic acid (thiophene-2-carbonyl)-amide (64)**



LC/MS System C: $R_t = 4.06\text{mins}$, m/z (ES^-) = 452 ((M-H) for $\text{C}_{23}\text{H}_{19}\text{NO}_5\text{S}_2$).

10

Example 14F: Synthesis of 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulphonic acid (3-methoxy-propionyl)-amide (65)



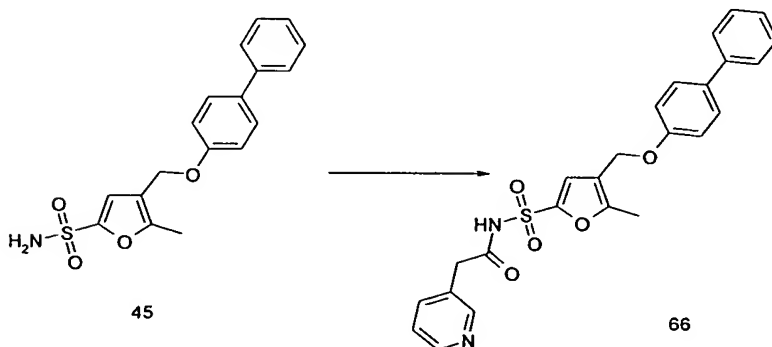
15

To a stirred solution of 4-(biphenyl-4-yloxymethyl)-5-

methyl-furan-2-sulphonic acid amide (**45**) (50mg, 0.146mmoles) in N,N-dimethylformamide (4.0ml) was added diisopropylethylamine (85 μ l, 0.480mmoles) then a solution of 3-methoxypropionic acid (14 μ l, 0.146mmoles) in N,N-dimethylformamide (1.0ml). O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (61mg, 0.160mmoles) in N,N-dimethylformamide (1.0ml) was added and the solution stirred at room temperature for 16 hours. The reaction mixture was concentrated *in-vacuo*, and the residue was purified by HPLC to give compound **65** as a white solid (42mg). LC/MS System A: R_t = 3.80mins, m/z (ES^-) = 428 ((M-H) for $C_{22}H_{23}NO_6S$).

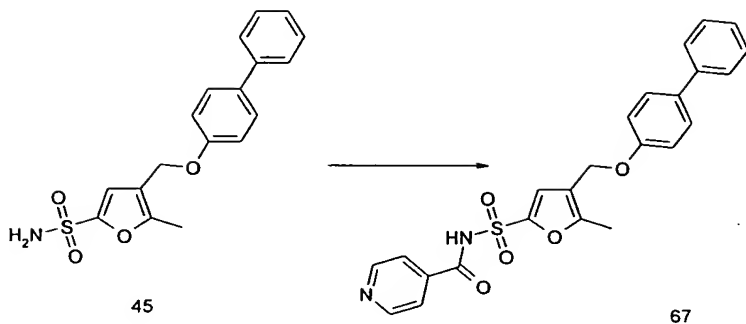
By adapting the procedure of Example 14F there were prepared Examples 14G to 14I:

Example 14G: 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulphonic acid (pyridin-3-yl-acetyl)-amide (66)



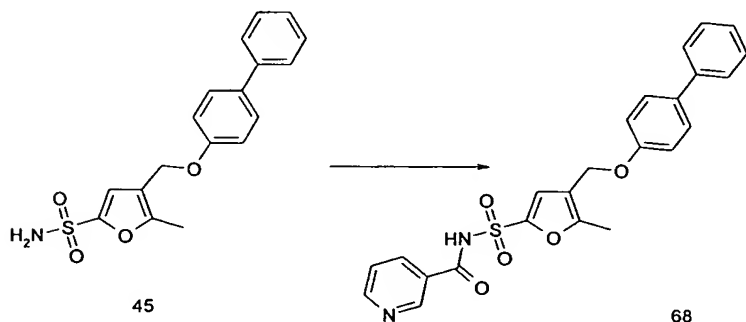
LC/MS System D: R_t = 5.64mins, m/z (ES^+) = 463 ((M+H) for $C_{25}H_{22}N_2O_5S$).

Example 14H: 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulphonic acid (pyridine-4-carbonyl)-amide (67)



LC/MS System D: $R_t = 5.85\text{mins}$, m/z (ES^+) = 449 ((M+H) for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_5\text{S}$).

5 **Example 14I: 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulphonic acid (pyridine-3-carbonyl)-amide (68)**



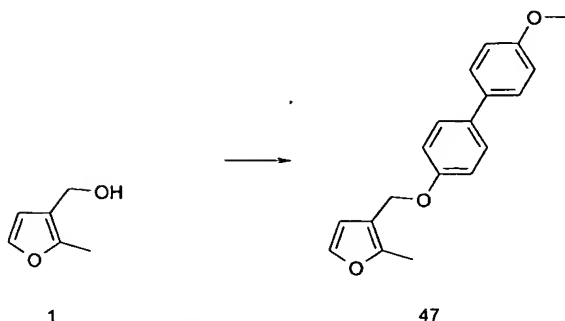
LC/MS System D: $R_t = 5.92\text{mins}$, m/z (ES^+) = 449 ((M+H) for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_5\text{S}$).

10

Example 15: Synthesis of 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid benzoylamide (49) and 4-(4'-Methoxy-biphenyl-4-yloxymethyl

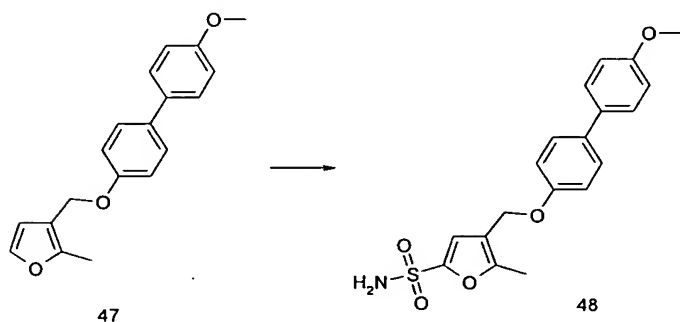
15 **1)-5-methyl-furan-2-sulfonic acid (3,5-dimethyl-isoxazole-4-carbonyl)-amide (69)**

(a) 3-(4'-Methoxy-biphenyl-4-yloxymethyl)-2-methyl-furan
(47)



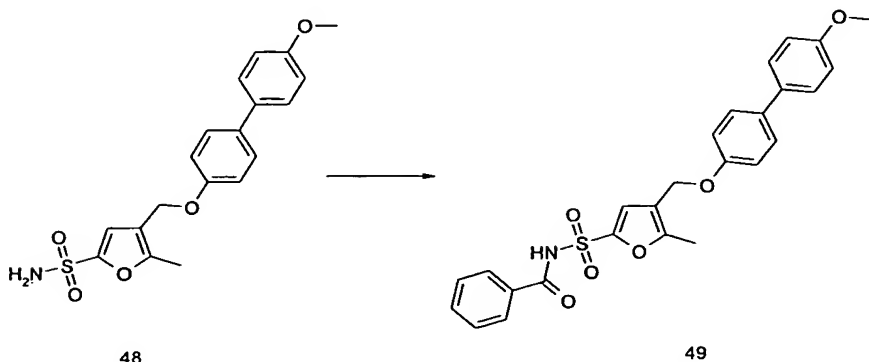
Compound 47 was prepared by adapting the procedure of
5 Example 14A(a). LC/MS System A: $R_t = 4.58$ mins.

(b) 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid amide (48)



10 Compound (48) was prepared from compound (47) by the
procedure of Example 14A(b). LC/MS System A: $R_t = 3.63$ mins.

(c) 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid benzoylamide (49)

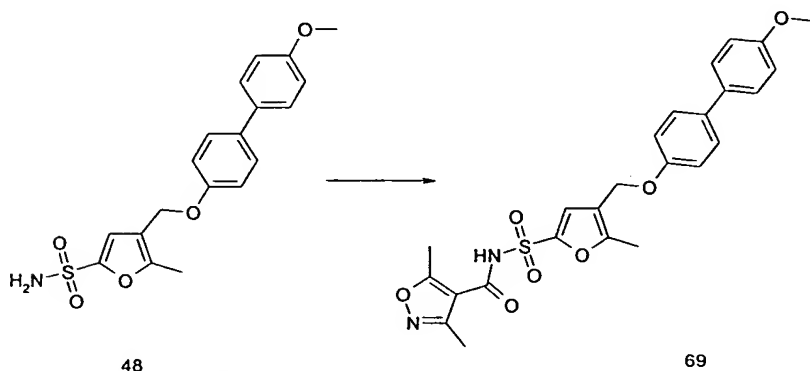


15

Compound (49) was prepared from compound (48) by the

procedure of Example 14B. LC/MS System C: $R_t = 5.37$ mins,
 m/z (ES^-) = 476 (M^- for $C_{26}H_{23}NO_6S$).

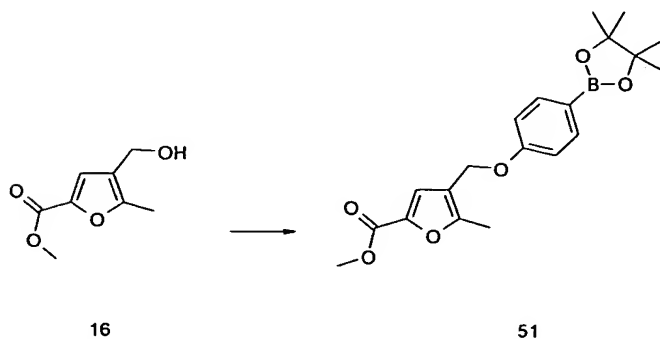
(d) 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
sulphonic acid (3,5-dimethyl-isoxazole-4-carbonyl)-amide
(69)



Compound (69) was prepared from compound (48) by adapting
the procedure of example 14B. LC/MS System C: $R_t = 4.45$
mins, m/z (ES^-) = 495 ($(M-H)$ for $C_{25}H_{24}N_2O_7S$).

**Example 16: Synthesis of 4-[4-(5-Methoxy-pyridin-2-yl)-
phenoxyethyl]-5-methyl-furan-2-carboxylic acid (53)**

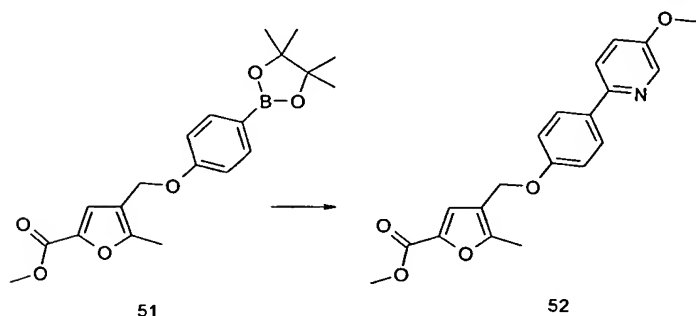
(a) 5-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-
2-yl)-phenoxyethyl]-furan-2-carboxylic acid methyl ester
(51)



A mixture of 4-hydroxymethyl-5-methyl-furan-2-carboxylic
acid methyl ester (16) (0.5g), 4-(4,4,5,5-tetramethyl-

[1,3,2]dioxaborolan-2-yl)-phenol (1.9g) and triphenylphosphine (2.3g) in dry tetrahydrofuran (20mL) under a nitrogen atmosphere was cooled to 0°C. Diisopropylazodicarboxylate (1.8mL) was added drop-wise and the mixture was stirred at room temperature for 72 hours. After concentrating *in vacuo*, the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was extracted with pentane and the pentane phase was decanted and concentrated to give compound **51** as an oil. This was used without further purification.

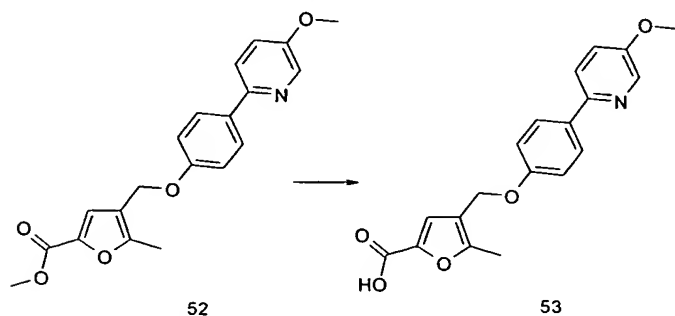
(b) 4-[4-(5-Methoxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-2-carboxylic acid methyl ester (**52**)



A mixture of 5-methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy-methyl]-furan-2-carboxylic acid methyl ester (**51**) (126mg), 2M aqueous cesium carbonate (0.6mL) and 2-iodo-5-methoxypyridine (95mg) in 1,4-dioxane (10mL) under an argon atmosphere was sonicated to expel traces of oxygen. [1,1'-Bis-(diphenylphosphino) ferrocene] dichloropalladium (II) (8mg) was added and the mixture heated at 95°C for 18 hours. After cooling, the mixture was acidified to pH6 with 1M aqueous hydrochloric acid and partitioned between ethyl acetate and water. The organic phase was dried (MgSO₄) and evaporated to give compound **52** as an oil (70mg), which was used directly in the next step.

LC/MS System A: $R_t = 3.23$ mins, $m/z = 354$ ((M+H) for $C_{20}H_{19}NO_5$).

(c) 4-[4-(5-Methoxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-2-carboxylic acid (**53**)



Method 1

A solution of 4-[4-(5-methoxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-2-carboxylic acid methyl ester (**52**) (118mg, 0.33mmoles) in dry tetrahydrofuran (10ml) was treated with potassium trimethylsilanoate (260mg, 2.0mmoles) and the mixture stirred under an argon atmosphere for 2 hours. After evaporation of the solvent the residue was purified by HPLC (gradient: 18% acetonitrile/82% water containing 0.1% trifluoroacetic acid to 98% acetonitrile/2% water at a rate of 1%/min) to afford compound **53** (60mg) as a white solid.

Method 2

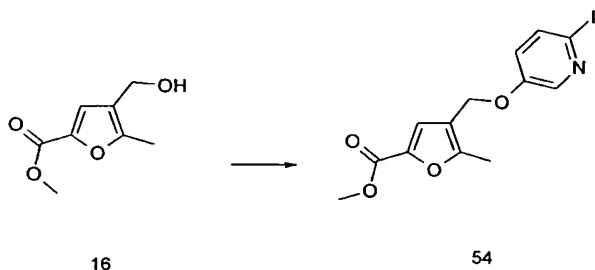
A mixture of 4-[4-(5-methoxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-2-carboxylic acid methyl ester (**52**) (70mg) and 1M aqueous lithium hydroxide (1mL) in tetrahydrofuran/methanol (2:1 by volume) (12mL) was stirred at room temperature for 16 hours. The reaction mixture was acidified to between pH6 and pH7, and partitioned between ethyl acetate and water. The organic phase was separated, washed with brine and dried ($MgSO_4$). After removal of the solvent, the residue was purified by HPLC. Compound **53** was obtained as a solid (2.5mg). LC/MS System A: $R_t = 2.90$ mins,

$$m/z \text{ (ES}^+) = 340 \text{ ((M+H) for C}_{19}\text{H}_{17}\text{NO}_5).$$

Example 17: Synthesis of 4-[6-(4-Methoxy-phenyl)-pyridin-3-yloxymethyl]-5-methyl-furan-2-carboxylic acid (56)

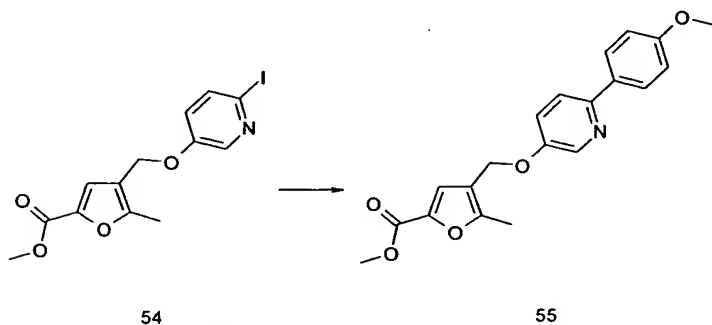
5

(a) 4-(6-iodo-pyridin-3-yloxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (54)



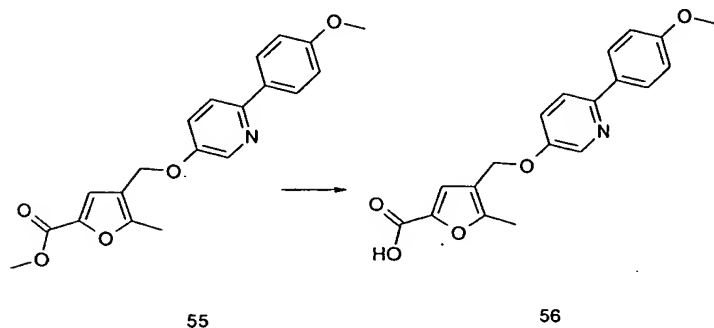
Compound (**54**) was prepared from compound (**16**) and 2-iodo-5-
10 hydroxy-pyridine in a manner analagous to that described in
Example 5(a). LC/MS System A: $R_t = 3.52$ mins, $m/z = 374$
($(M+H)$ for $C_{13}H_{12}INO_4$)

(b) 4-[6-(4-Methoxy-phenyl)-pyridin-3-yloxymethyl]-5-methyl-
15 furan-2-carboxylic acid methyl ester (**55**)



Compound (55) was prepared from compound (54) by adapting the procedure of Example 5(b). LC/MS System A: R_t = 3.37 mins, m/z = 354 ((M+H) for $C_{20}H_{19}NO_5$).

(c) 4-[6-(4-Methoxy-phenyl)-pyridin-3-yloxymethyl]-5-methyl-furan-2-carboxylic acid (**56**)

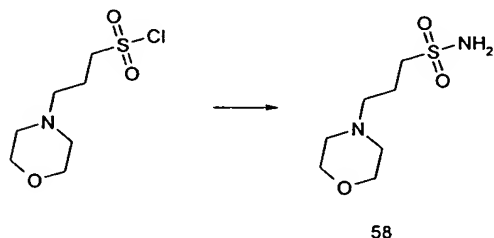


Compound (**56**) was prepared from compound (**55**) by adapting
5 the procedure of Example 16(c). LC/MS System A: $R_t = 2.79$
mins, m/z (ES^+) = 340 ($(M+H)$ for $C_{19}H_{17}NO_5$)

Example 18: Synthesis of 3-Morpholin-4-yl-propane-1-sulphonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (59**)**

10

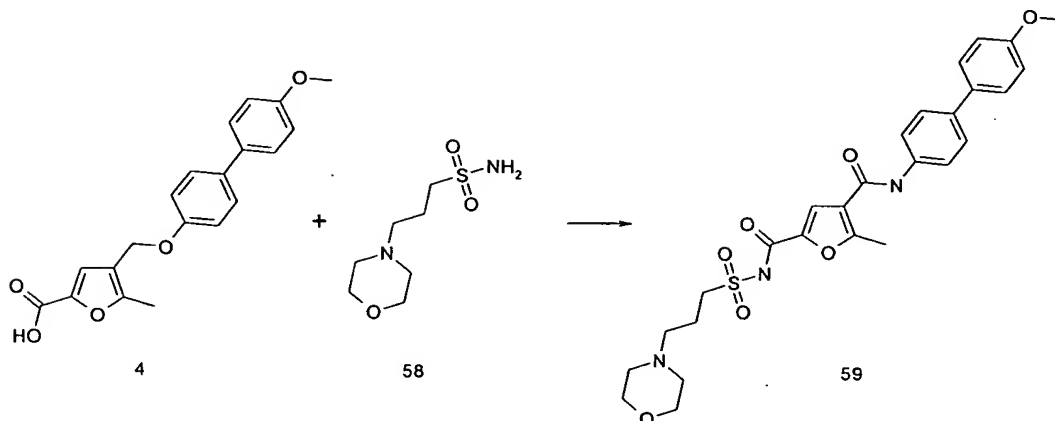
(a) 3-Morpholin-4-yl-propane-1-sulfonic acid amide (**58**)



Dichloromethane (40ml) was saturated with ammonia gas with
15 cooling (dry ice /acetone), and then 3-morpholin-4-yl-
propane-1-sulphonyl chloride (279mg, 1.23mmoles) was added.
The mixture was stirred at room temperature for 24 hours.
The mixture was filtered, the filtrate evaporated and the
residue was dried at 40°C in vacuo to afford compound **58**
20 (210mg) as a gum. LC/MS System A; $R_t = 0.28$ mins, m/z (ES^+)
= 209 ($M+H$ for $C_7H_{16}N_2O_3S$).

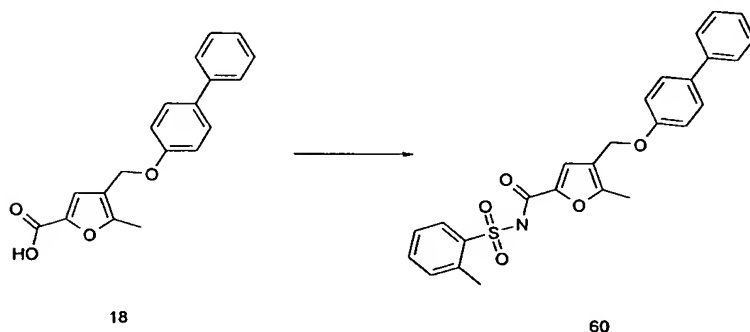
(b) 3-Morpholin-4-yl-propane-1-sulphonic acid [4-(4'-

methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (59)



Compound (59) was prepared from compounds (4) and (58) by
 5 adapting the procedure of Example 2A. LC/MS System D; R_t =
 4.97mins, m/z (ES^+) = 529 ($M+H$ for $C_{27}H_{32}N_2O_7S$).

Example 19: Synthesis of N-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-2-methyl-benzenesulphonamide (60)



10

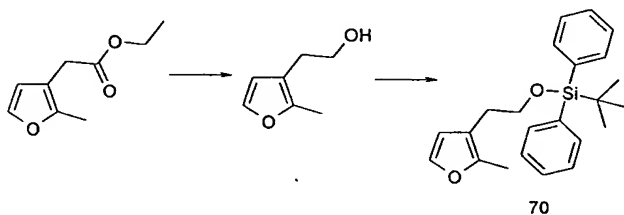
15

A stirred solution of 4-(biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (18) (50mg, 0.162mmoles), 2-methyl-benzenesulphonamide (42mg, 0.243mmoles) and 4-(N,N-dimethylamino)-pyridine (2.5mg) in a mixture of tetrahydrofuran (8ml) and acetonitrile (2ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (38mg, 0.194mmoles). The mixture was stirred at room temperature for 16 hours under an argon atmosphere. The reaction mixture was concentrated *in vacuo* and the

residue was purified by HPLC to afford compound **60** (20mg) as a white solid. LC/MS System D; R_t = 11.09mins, m/z (ES^+) = 462 ($M+H$ for $C_{26}H_{23}NO_5S$).

5 **Example 20A: Synthesis of 4-[2-(Biphenyl-4-yloxy)-ethyl]-5-methyl-furan-2-carboxylic acid (72)**

(a) *tert*-Butyl-[2-(2-methyl-furan-3-yl)-ethoxy]-diphenyl-silane (**70**)

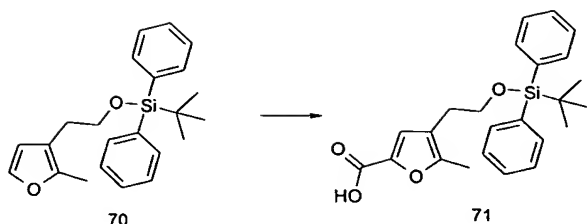


- 10 (i) A solution of (2-methyl-furan-3-yl)-acetic acid ethyl ester (11.8g, 70.2mmoles) in tetrahydrofuran (50ml) was added to a stirred suspension of lithium aluminium hydride (2.66g, 70.2mmoles) under a nitrogen atmosphere and with cooling to 0°C. When the addition was complete the mixture was stirred at room temperature for 3 hours, then quenched by the addition of excess acetone. After acidifying with 10% aqueous hydrochloric acid the mixture was extracted three times with diethyl ether. The combined extracts were dried and evaporated to afford crude 2-(2-methyl-furan-3-yl)-ethanol as a yellow oil.
- 15
- 20

(ii) Compound (**70**) was prepared in the form of a pale yellow oil from crude 2-(2-methyl-furan-3-yl)-ethanol (from (i)) by adapting the procedure of Example 1(a).

25

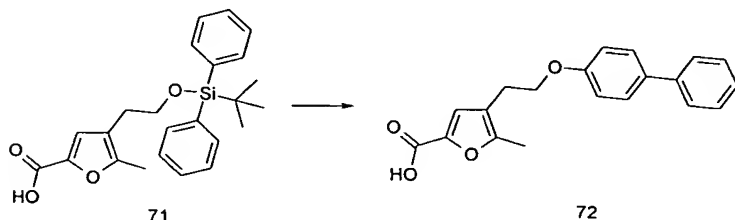
(b) 4-[2-(*tert*-Butyl-diphenyl-silanyloxy)-ethyl]-5-methyl-furan-2-carboxylic acid (**71**)



Compound (**71**) was prepared in the form of a pale yellow oil from compound (**70**) by adapting the procedure of Example 1(b).

5

(c) 4-[2-(Biphenyl-4-yloxy)-ethyl]-5-methyl-furan-2-carboxylic acid (**72**)

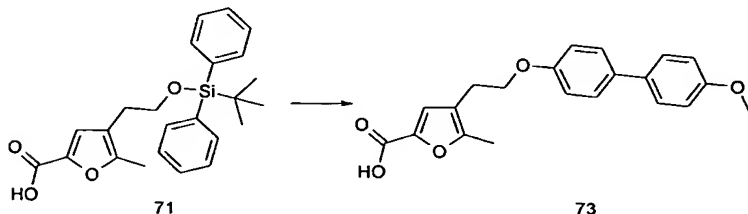


Compound (**72**) was prepared from compound (**71**) in an analogous manner to the methods described in Example 1(c). LC/MS System B: $R_t = 1.86$ mins, m/z (ES^-) = 321 ((M-H) for $C_{20}H_{18}O_4$).

10

Example 20B: Synthesis of 4-[2-(4'-Methoxy-biphenyl-4-yloxy)-ethyl]-5-methyl-furan-2-carboxylic acid (73**)**

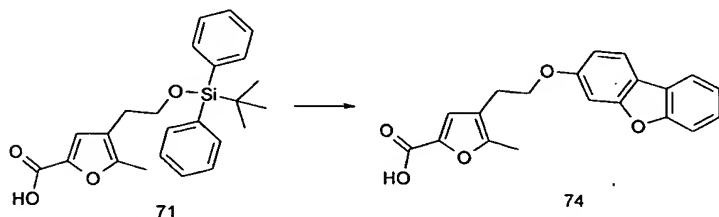
15



Compound (**73**) was prepared from compound (**71**) in an analogous manner to the methods described in Example 1(c). LC/MS System B: $R_t = 1.86$ mins, m/z (ES^-) = 351 ((M-H) for $C_{21}H_{20}O_5$).

20

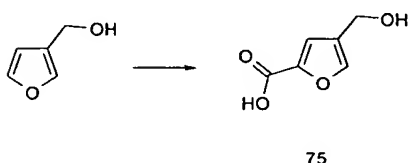
Example 20C: Synthesis of 4-[2-(Dibenzofuran-3-yloxy)-ethyl]-5-methyl-furan-2-carboxylic acid (74)



Compound (**74**) was prepared from compound (**71**) in an analogous manner to the methods described in Example 1(c). LC/MS System B: $R_t = 1.86\text{mins}$, m/z (ES^-) = 335 ($(\text{M}-\text{H})$ for $\text{C}_{20}\text{H}_{16}\text{O}_5$).

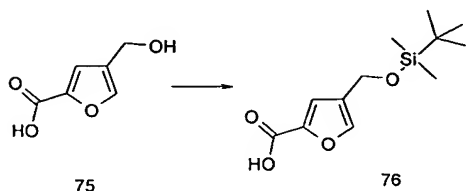
Example 21A: Synthesis of 4-(Biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (77)

(a) 4-Hydroxymethyl-furan-2-carboxylic acid (**75**)



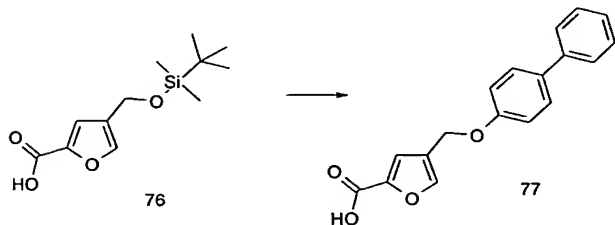
A solution of furan-3-yl-methanol (1.6g, 16.5mmoles) in dry tetrahydrofuran (25ml) under an argon atmosphere was cooled to -78°C and treated dropwise with n-butyl-lithium (9.2mL, 23mmoles of a 2.5M solution in hexanes). After 1 hour, sec-butyl-lithium (14.0ml, 18.2mmoles of a 1.3M solution in hexanes) was added. After stirring for a further 4 hours at -78°C , the mixture was quenched by the addition of a large excess of solid carbon dioxide. The mixture was allowed to warm to room temperature and was added to a mixture of ethyl acetate and 1M aqueous hydrochloric acid (60ml). The organic phase was separated, washed with brine, dried, and evaporated. The residue was dissolved in dichloromethane and on standing a cream solid precipitated. The precipitate was collected and dried to afford compound **75** as cream solid (0.4g).

(b) 4-(*tert*-Butyl-dimethyl-silyloxymethyl)-furan-2-carboxylic acid (**76**)



5 A mixture of 4-hydroxymethyl-furan-2-carboxylic acid (**75**)
(1.4g, 9.85mmoles), *tert*-butyl-chloro-dimethyl-silane (3.2g,
21mmoles) and imidazole (2.14g, 31.5mmoles) in dry DMF
(35ml) was stirred at room temperature for 24 hours. Excess
methanol (~3ml) was added and the mixture stirred for a
10 further 3 hours. After partitioning between ethyl acetate
and water, the aqueous phase was acidified to pH = 1 with 2M
aqueous hydrochloric acid and re-extracted with ethyl
acetate. The combined ethyl acetate phases were washed with
water, dried (MgSO₄), and the solvent evaporated to give
15 compound **76** as a white solid (2.4g).

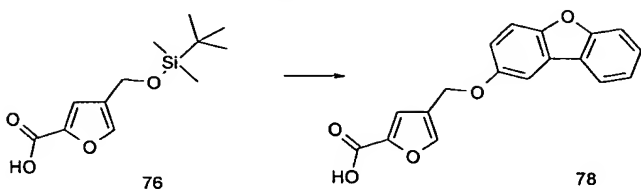
(c) 4-(Biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (**77**)



20 Compound (**77**) was prepared from compound (**76**) in an
analogous manner to the methods described in Example 1(c).
LC/MS System B; R_t = 1.72mins, m/z (ES⁻) = 293 (M-H for
C₁₈H₁₄O₄).
25

Example 21B: Synthesis of 4-(Dibenzofuran-2-yloxymethyl)-

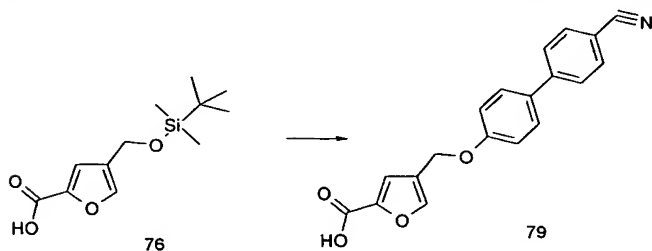
furan-2-carboxylic acid (78)



Compound **(78)** was prepared from compound **(76)** in an analogous manner to the methods described in Example 1(c).

LC/MS System B; $R_t = 1.72\text{mins}$, m/z (ES^-) = 307 ($\text{M}-\text{H}$ for $\text{C}_{18}\text{H}_{12}\text{O}_5$).

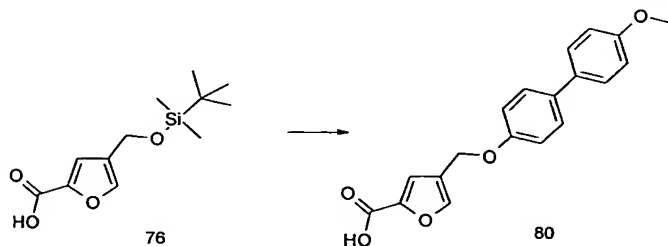
Example 21C: Synthesis of 4-(4'-Cyano-biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (79)



Compound **(79)** was prepared from compound **(76)** in an analogous manner to the methods described in Example 1(c).

LC/MS System B; $R_t = 1.65\text{mins}$, m/z (ES^-) = 318 ($\text{M}-\text{H}$ for $\text{C}_{19}\text{H}_{13}\text{NO}_4$).

Example 21D: Synthesis of 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (80)

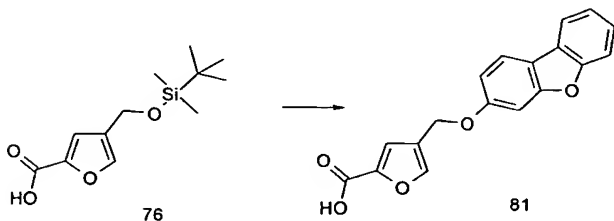


Compound **(80)** was prepared from compound **(76)** in an analogous manner to the methods described in Example 1(c).

LC/MS System B; $R_t = 1.72\text{mins}$, m/z (ES^-) = 323 ($\text{M}-\text{H}$ for

C₁₉H₁₆O₅).

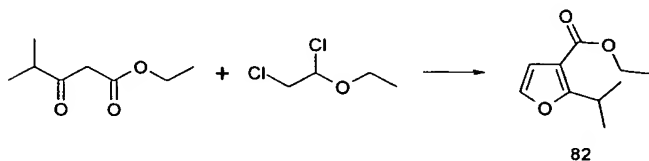
Example 21E: Synthesis of 4-(Dibenzofuran-3-yloxymethyl)-furan-2-carboxylic acid (81)



Compound (81) was prepared from compound (76) in an analogous manner to the methods described in Example 1(c). LC/MS System B; R_t = 1.75mins, m/z (ES⁻) = 307 (M-H for C₁₈H₁₂O₅).

Example 22A: Synthesis of 4-(Biphenyl-4-yloxymethyl)-5-isopropyl-furan-2-carboxylic acid (85)

(a) 2-Isopropyl-furan-3-carboxylic acid ethyl ester (82)

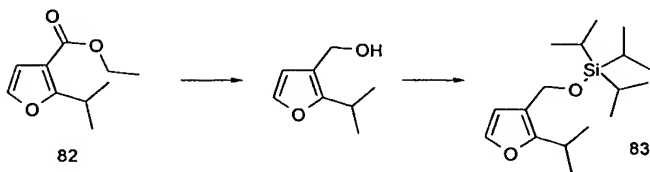


15 An ice-chilled solution of sodium hydroxide (1.9g) in water (25ml) was added, during 40 minutes, to a stirred solution of 4-methyl-3-oxo-pentanoic acid ethyl ester (3g, 18.96mmoles) and 1,2-dichloro-1-ethoxy-ethane (3.3g, 35.19mmole) in diethyl ether (15ml) with ice bath cooling.

20 When the addition was complete the mixture was stirred rapidly for 1 hour, then the ethereal layer was separated, washed with water and dried. Evaporation of the solvent gave a yellow oil, which was purified by flash chromatography using a gradient elution from neat pentane to

25 pentane/diethyl ether 9:1 v/v as eluent, to afford compound 82 as an oil (2.4g).

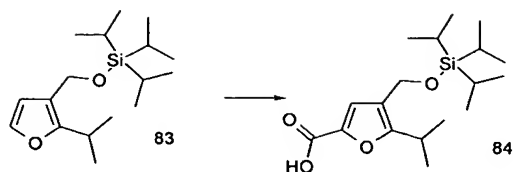
(b) *Tri-isopropyl-(2-isopropyl-furan-3-ylmethoxy)-silane*
(**83**)



(i) A solution of 2-isopropyl-furan-3-carboxylic acid ethyl ester (**82**) (4.0g, 21.95mmoles) in tetrahydrofuran (70ml) was treated portionwise during 0.5h with lithium aluminium hydride (0.7g, 18.4mmoles) under a nitrogen atmosphere. When the addition was complete the mixture was stirred at room temperature for 18 hours, then quenched by the addition of excess acetone (1ml) and then water (1ml). After diluting with ethyl acetate (150ml) the grey precipitate was removed by filtration. The filtrate was evaporated and the residue dissolved in diethyl ether and dried. Evaporation of the solvent afforded (2-isopropyl-furan-3-yl)-methanol. This material was used immediately in the next step.

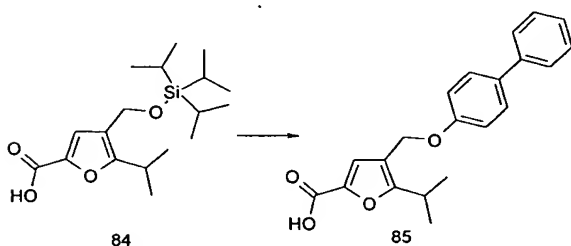
(ii) A solution of the (2-isopropyl-furan-3-yl)-methanol from (i) in dry dichloromethane (120ml) was treated with chloro-tri-isopropyl-silane (5.2g, 27.0mmoles) and imidazole (3.0g, 44.0mmoles) and the mixture was stirred overnight at room temperature. The reaction mixture was washed sequentially with 2M aqueous hydrochloric acid, water, saturated aqueous sodium bicarbonate, water and brine. After drying, evaporation of the solvents afforded a colourless oil, which heated at 125°C under reduced pressure (10millibars). The residue was compound **83** obtained as a pale yellow oil.

(c) *5-Isopropyl-4-triisopropylsilanyloxymethyl-furan-2-carboxylic acid* (**84**)



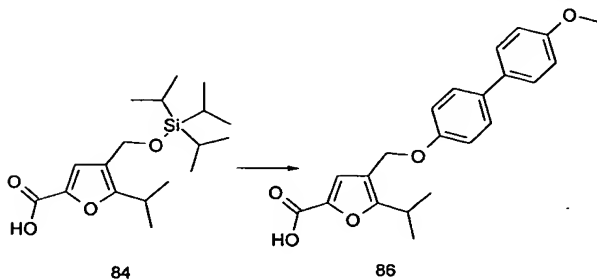
Compound (**84**) was prepared in the form of a cream solid from compound (**83**) by adapting the procedure of Example 1(b).

5 (d) 4-(Biphenyl-4-yloxymethyl)-5-isopropyl-furan-2-carboxylic acid (**85**)



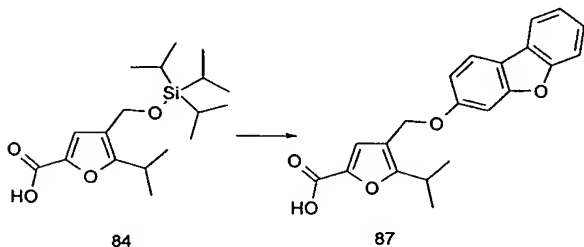
Compound (**85**) was prepared from compound (**84**) in an analogous manner to the methods described in Example 1(c).
LC/MS System B; $R_t = 1.93\text{mins}$, m/z (ES^-) = 335 (M-H for $\text{C}_{21}\text{H}_{20}\text{O}_4$).

15 **Example 22B: Synthesis of 5-Isopropyl-4-(4'-methoxy-biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (**86**)**



Compound (**86**) was prepared from compound (**84**) in an analogous manner to the methods described in Example 1(c).
LC/MS System B; $R_t = 1.93\text{mins}$, m/z (ES^-) = 365 (M-H for $\text{C}_{22}\text{H}_{22}\text{O}_5$).

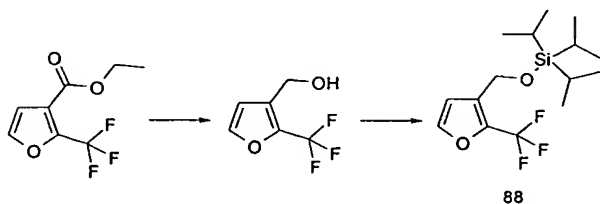
Example 22C: Synthesis of 4-(Dibenzofuran-3-yloxymethyl)-5-isopropyl-furan-2-carboxylic acid (87)



5 Compound (**87**) was prepared from compound (**84**) in an analogous manner to the methods described in Example 1(c). LC/MS System B; $R_t = 1.93$ mins, m/z (ES^-) = 349 ($M-H$ for $C_{21}H_{18}O_5$).

10 **Example 23A: Synthesis of 4-(Biphenyl-4-yloxymethyl)-5-trifluoromethyl-furan-2-carboxylic acid (90)**

(a) *Tri-isopropyl-(2-trifluoromethyl-furan-3-ylmethoxy)-silane (88)*



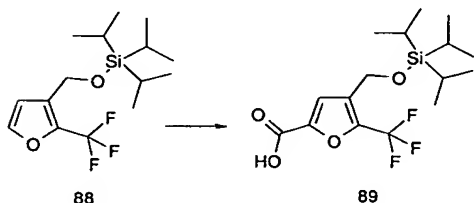
15 (i) A solution of 2-trifluoromethyl-furan-3-carboxylic acid ethyl ester (2.2g, 10.5mmoles) in tetrahydrofuran (150ml) was treated portionwise during 0.5h with lithium aluminium hydride (0.55g, 14.5mmoles) under a nitrogen atmosphere. When the addition was complete the mixture was stirred at
20 room temperature for 18h, then quenched by the addition of excess acetone (1ml) and then water (1ml). After diluting with ethyl acetate (200ml) the grey precipitate was removed by filtration. The filtrate was dried and evaporation of the solvent afforded (2-trifluoromethyl-furan-3-yl)-methanol as
25 a colourless oil. This material was used immediately in the

next step.

(ii) A solution of the (2-trifluoromethyl-furan-3-yl)-methanol from (i) in dry dichloromethane (180ml) was treated with chloro-tri-isopropyl-silane (2.6g, 13.4mmoles) and imidazole (1.45g, 21.3mmoles) and the mixture was stirred overnight at room temperature. Further aliquots of chloro-tri-isopropyl-silane (0.9g, 4.64mmoles) and imidazole (0.5g, 7.34mmoles) were added and the mixture was stirred for 3h.

The reaction mixture was diluted with water, the organic phase separated and washed sequentially with 0.1M aqueous hydrochloric acid, water, saturated aqueous sodium bicarbonate, water and brine. After drying, evaporation of the solvents afforded a colourless oil. The oil was distilled under reduced pressure (0.05torr) in a Kugelrohr apparatus collecting the fraction boiling at an oven temperature of $125 \pm 20^\circ\text{C}$ to afford compound **88** as a colourless oil.

(b) 5-Trifluoromethyl-4-triisopropylsilanyloxymethyl-furan-2-carboxylic acid (**89**)



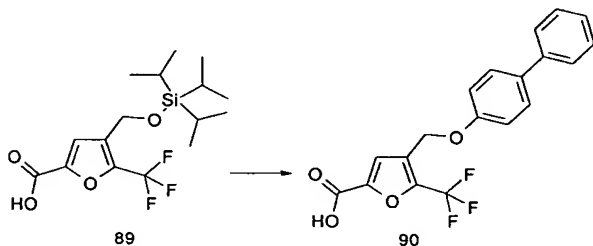
A stirred solution of tri-isopropyl-(2-trifluoromethyl-furan-3-ylmethoxy)-silane (**88**) (2.0g, 6.24mmoles) in

tetrahydrofuran (70ml) under argon was cooled to -78°C and treated with sec-butyl-lithium (2.2ml, 2.86mmoles of a 1.3M solution in cyclohexane). After 1h at -78°C , excess solid carbon dioxide, which had been pre-washed with tetrahydrofuran, was added and the mixture was allowed to warm to room temperature. The mixture was acidified to pH= 4

with dilute aqueous hydrochloric acid and extracted several times with ethyl acetate. The combined extracts were dried (MgSO_4) and solvent removed to afford compound (89) as an off-white solid (1.2g).

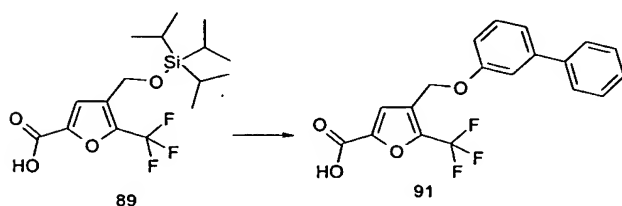
5

(c) 4-(Biphenyl-4-yloxymethyl)-5-trifluoromethyl-furan-2-carboxylic acid (90)



10 Compound (90) was prepared from compound (89) in an analogous manner to the methods described in Example 1(c). The product was purified by HPLC. LC/MS System B; R_t = 1.97mins, m/z (ES^-) = 361 ($\text{M}-\text{H}$ for $\text{C}_{19}\text{H}_{13}\text{F}_3\text{O}_4$).

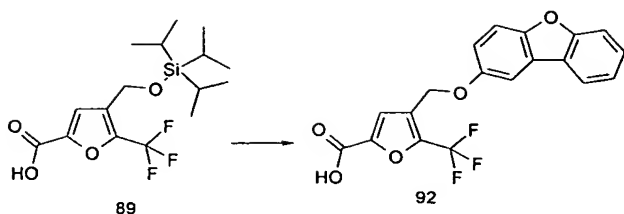
15 **Example 23B: Synthesis of 4-(Biphenyl-3-yloxymethyl)-5-trifluoromethyl-furan-2-carboxylic acid (91)**



Compound (91) was prepared from compound (89) in an analogous manner to the methods described in Example 1(c).

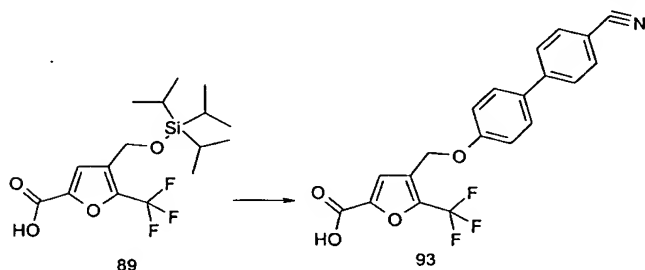
20 The product was purified by HPLC. LC/MS System B; R_t = 1.97mins, m/z (ES^-) = 361 ($\text{M}-\text{H}$ for $\text{C}_{19}\text{H}_{13}\text{F}_3\text{O}_4$).

Example 23C: Synthesis of 4-(Dibenzofuran-2-yloxymethyl)-5-trifluoromethyl-furan-2-carboxylic acid (92)



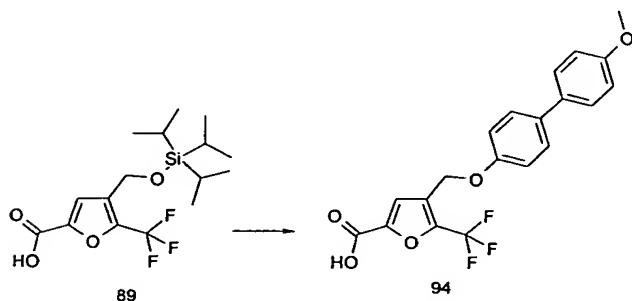
Compound **(92)** was prepared from compound **(89)** in an analogous manner to the methods described in Example 1(c). The product was purified by HPLC. LC/MS System B; $R_t =$
5 1.97mins, m/z (ES^-) = 375 ($M-H$ for $C_{19}H_{11}F_3O_5$).

Example 23D: 4-(4'-Cyano-biphenyl-4-yloxymethyl)-5-trifluoromethyl-furan-2-carboxylic acid (93)



10 Compound **(93)** was prepared from compound **(89)** in an analogous manner to the methods described in Example 1(c). The product was purified by HPLC. LC/MS System B; $R_t =$
1.89mins, m/z (ES^-) = 386 ($M-H$ for $C_{20}H_{12}F_3NO_4$).

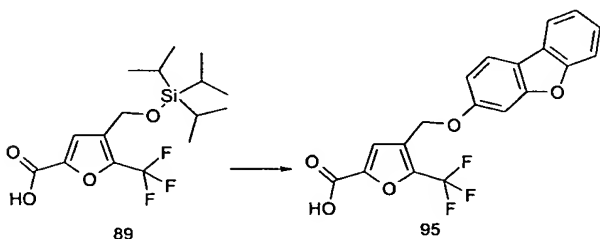
15 **Example 23E: Synthesis of 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-trifluoromethyl-furan-2-carboxylic acid (94)**



Compound **(94)** was prepared from compound **(89)** in an analogous manner to the methods described in Example 1(c).

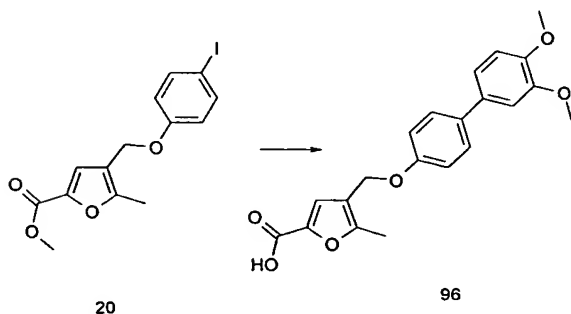
The product was purified by HPLC. LC/MS System B; R_t = 1.97mins, m/z (ES^-) = 391 ($M-H$ for $C_{20}H_{15}F_3O_5$).

Example 23F: 4-(Dibenzofuran-3-yloxymethyl)-5-trifluoromethyl-furan-2-carboxylic acid (95)



Compound (95) was prepared from compound (89) in an analogous manner to the methods described in Example 1(c). The product was purified by HPLC. LC/MS System B; R_t = 1.97mins, m/z (ES^-) = 375 ($M-H$ for $C_{19}H_{11}F_3O_5$).

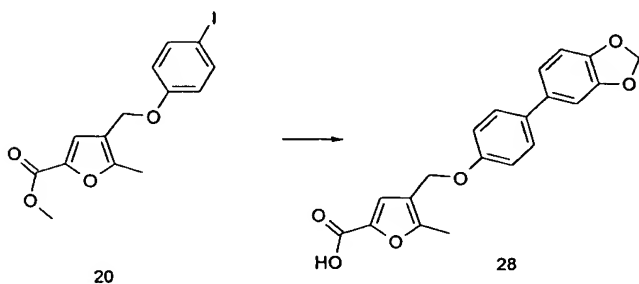
Example 24A: Synthesis of 4-(3',4'-Dimethoxy-biphenyl-4-yloxy methyl)-5-methyl-furan-2-carboxylic acid (96)



A stirred mixture of 4-(4-iodo-phenoxy)methyl)-5-methyl-furan-2-carboxylic acid methyl ester (20) (0.025g, 0.067mmoles), (3,4-dimethoxyphenyl)-boronic acid (0.017g, 0.093mmoles), N,N -dimethylformamide (3mL), potassium acetate (0.026g) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (4 mg) was stirred at room temperature under an argon atmosphere for 24h. The reaction mixture was diluted with water and extracted with ethyl

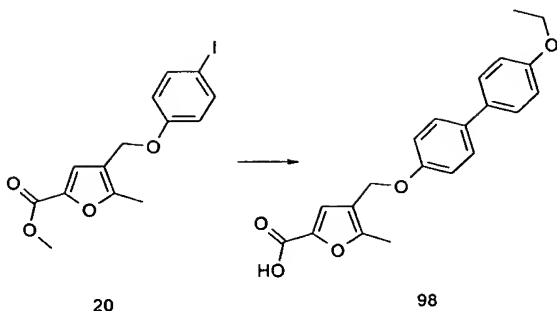
acetate. The extracts were washed with water, dried and concentrated *in vacuo*. The residue was dissolved in a mixture of tetrahydrofuran/methanol (2:1 by volume) (2.5mL) and 1.0 M aqueous lithium hydroxide solution (0.5 mL), and stirred for 16 hours. The reaction mixture was acidified to pH=6 using 1M hydrochloric acid and extracted with ethyl acetate (3 x 25 mL). The extracts were dried, concentrated *in vacuo* and the residue purified by HPLC (gradient: 30% acetonitrile/70% water containing 0.1% trifluoroacetic acid to 70% acetonitrile/30% water at a rate of 1%/min) to give compound **96** as a solid (15mg). LC/MS System B; R_t = 1.65mins, m/z (ES^-) = 367 ($M-H$ for $C_{21}H_{20}O_6$).

Example 24B: Alternate synthesis of 4-(4-Benzo[1,3]dioxol-5-yl-phenoxyethyl)-5-methyl-furan-2-carboxylic acid (28)



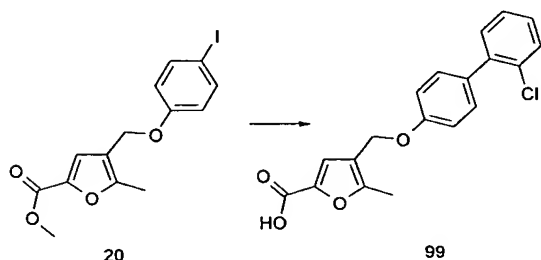
Compound (28) was prepared from compound (20) and (3,4-methylenedioxyphenyl)-boronic acid by adapting the procedure of Example 24A. LC/MS System B; R_t = 1.76mins, m/z (ES^-) = 351 ($M-H$ for $C_{20}H_{16}O_6$).

Example 24C: 4-(4'-Ethoxy-biphenyl-4-yloxyethyl)-5-methyl-furan-2-carboxylic acid (98)



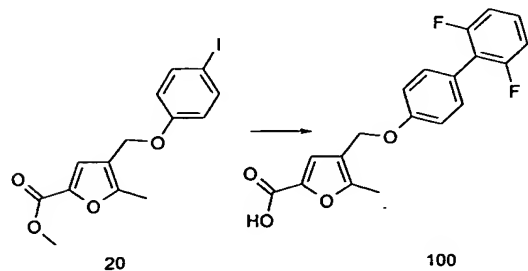
Compound (98) was prepared from compound (20) and (4-ethoxyphenyl)-boronic acid by an adapting the procedure of Example 24A. LC/MS System B; $R_t = 1.86$ mins, m/z (ES^-) = 351 (M-H for $C_{21}H_{20}O_5$).

Example 25A: Synthesis of 4-(2'-Chloro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (99)



Compound (99) was prepared from compound (20) and (2-chlorophenyl)-boronic acid by adapting the procedure of Example 5(b). LC/MS System B; $R_t = 1.86$ mins, m/z (ES^-) = 341 and 343 (M-H for $C_{19}H_{15}ClO_4$).

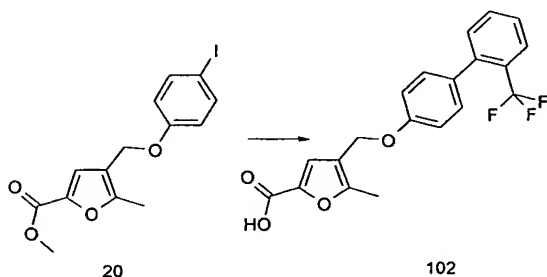
Example 25B: Synthesis of 4-(2',6'-Difluoro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (100)



Compound (100) was prepared from compound (20) and (2,6-

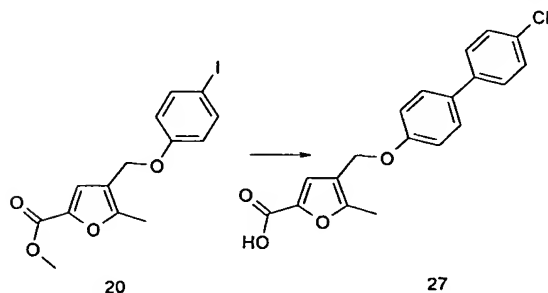
difluorophenyl)-boronic acid by adapting the procedure of Example 5(b). LC/MS System B; $R_t = 1.83$ mins, m/z (ES^-) = 343 (M-H for $C_{19}H_{14}F_2O_4$).

5 **Example 25C: Synthesis of 5-Methyl-4-(2'-trifluoromethyl-biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (102)**



Compound (**102**) was prepared from compound (**20**) and (2-trifluoromethyl-phenyl)-boronic acid by adapting the
10 procedure of Example 5(b). LC/MS System B; $R_t = 1.93$ mins, m/z (ES^-) = 375 (M-H for $C_{20}H_{15}F_3O_4$).

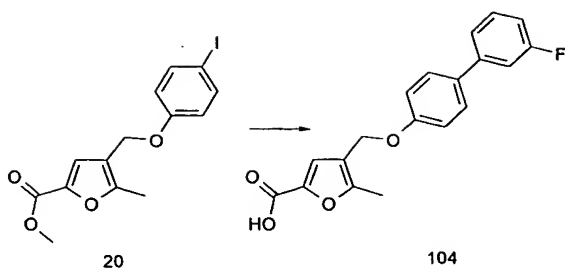
Example 25D: Alternate synthesis of 4-(4'-Chloro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (27)



15 Compound (**77**) was prepared from compound (**20**) and (4-chloro-phenyl)-boronic acid by adapting the procedure of Example 5(b). LC/MS System B; $R_t = 1.93$ mins, m/z (ES^-) = 341 and 343 (M-H for $C_{19}H_{15}ClO_4$).

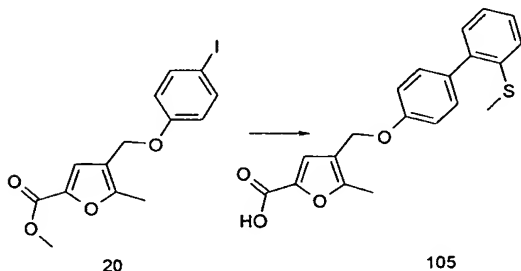
20

Example 25E: Synthesis of 4-(3'-Fluoro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (104)



Compound (104) was prepared from compound (20) and (3-fluoro-phenyl)-boronic acid by adapting the procedure of Example 5(b). LC/MS System B; $R_t = 1.83$ mins, m/z (ES^-) = 325 ($M-H$ for $C_{19}H_{15}FO_4$).

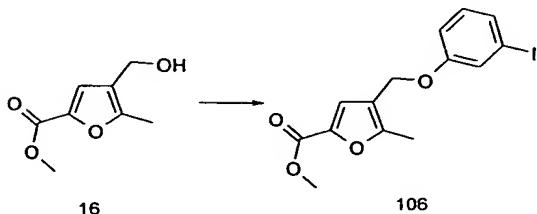
Example 25F: 5-Methyl-4-(2'-methylsulphanyl-biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (105)



Compound (105) was prepared from compound (20) and (2-methylsulphanyl-phenyl)-boronic acid by adapting the procedure of Example 5(b). LC/MS System B; $R_t = 1.86$ mins, m/z (ES^-) = 353 ($M-H$ for $C_{20}H_{18}O_4S$).

Example 26A: Synthesis of 4-(3',4'-Dimethoxy-biphenyl-3-yloxymethyl)-5-methyl-furan-2-carboxylic acid (108)

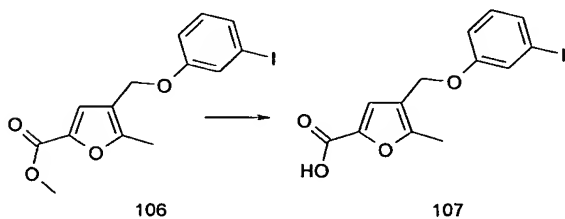
(a) 4-(3-Iodo-phenoxy)methyl-5-methyl-furan-2-carboxylic acid methyl ester (106)



A mixture of 4-hydroxymethyl-5-methyl-furan-2-carboxylic acid methyl ester (**16**) (1.85g, 10.9mmoles), 3-iodophenol (3.6g, 16.35mmoles), triphenylphosphine (4.3g, 16.35mmoles) in tetrahydrofuran (15mL) was cooled to 0°C.

5 Diisopropylazodicarboxylate (3.3g, 16.35mmoles) was added and the mixture was allowed to warm to room temperature, then stirred for 72h. The tetrahydrofuran was evaporated and the residue purified by flash chromatography using
10 hexane/ethyl acetate 7:3v/v as eluent to give compound **106** (2.8g). This was used directly in step (b).

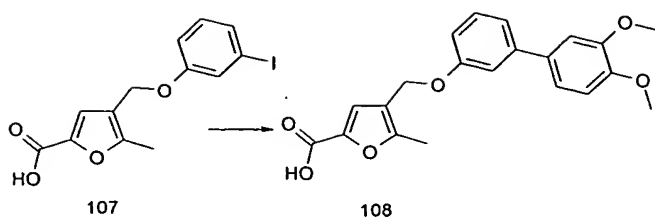
(b) 4-(3-Iodo-phenoxy-methyl)-5-methyl-furan-2-carboxylic acid (**107**)



15 A mixture of 4-(3-iodo-phenoxy-methyl)-5-methyl-furan-2-carboxylic acid methyl ester (**106**) (2.7g, 7.25mmoles) and lithium hydroxide (1.5g, 36.25mmoles) in tetrahydrofuran (25ml) containing water (2ml) was stirred at room
20 temperature for 3h. The tetrahydrofuran was evaporated, the residue was diluted with water and the mixture acidified to pH=1 with 1M aqueous hydrochloric acid. The precipitate was collected washed with water and dried at 70°C *in vacuo* to
give compound **107** (1.76g) as a white solid. LC/MS System B; $R_t = 3.51$ mins, m/z (ES^-) = 357 ($M-H$ for $C_{13}H_{11}IO_4$).

25

(c) 4-(3',4'-Dimethoxy-biphenyl-3-yloxy-methyl)-5-methyl-furan-2-carboxylic acid (**108**)



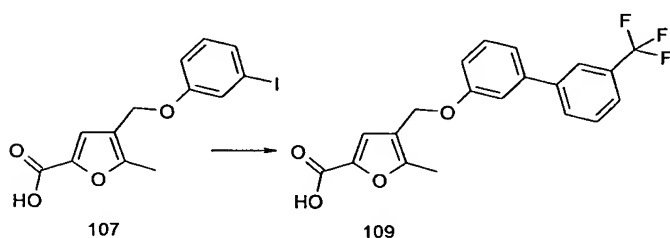
- (i) 2-Chlorotrityl chloride resin (2.5g of nominal loading 1.3 mmol/g) was swelled with dichloromethane (120 mL). After draining, a solution of 4-(3-iodo-phenoxy)methyl-5-methyl-furan-2-carboxylic acid (**107**) (1.16g, 3.24 mmoles) and diisopropylethylamine (2.25 mL, 12.96mmoles) in dichloromethane (20mL) was added and the mixture was shaken at ambient temperature for 72 hours. The resin was drained, washed sequentially with
- 10 dichloromethane/triethylamine/methanol (20:1:3 by volume) (3 x 30 mL), dichloromethane (4 x 30 mL), N,N-dimethylformamide (4 x 30 mL), dichloromethane (6 x 30 mL), and diethyl ether (3 x 30 mL) and then dried at 40°C *in vacuo*.
- 15 (ii) The loaded resin (110mg) from (i) was treated with a mixture of (3,4-dimethoxyphenyl)-boronic acid (119.7mg, 0.65mmoles), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (10.6mg) and potassium acetate (0.064g, 0.65mmoles) in
- 20 N,N-dimethylformamide (5mL) and the mixture was agitated at 100°C for 24 hours. The resin was drained, washed sequentially with tetrahydrofuran/water(1:1v/v) (2 x 5mL), tetrahydrofuran (2 x 5mL), N,N-dimethylformamide (3 x 5mL), dichloromethane (6 x 5mL) and diethyl ether (2 x 5ml), then
- 25 dried at 45°C *in vacuo*.

The resin was treated with dichloromethane/trifluoroacetic acid (19:1 by volume) (3mL) for 30 mins and the solution drained from the resin. This procedure was repeated. The

30 combined solutions were concentrated *in vacuo* and the

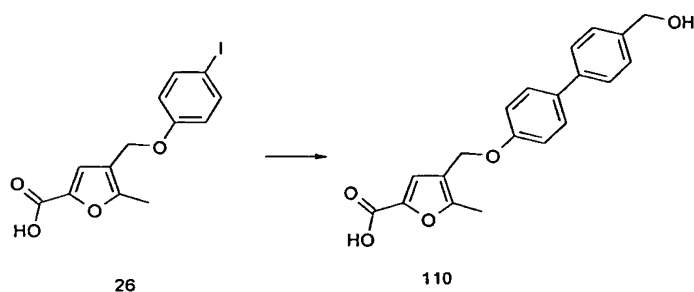
residue purified by hplc (gradient: 30% acetonitrile/70% water containing 0.1% trifluoroacetic acid to 90% acetonitrile/10% water at a rate of 1%/min) to afford compound **108** (24.9mg) as a solid. LC/MS System B; R_t = 1.69mins, m/z (ES^-) = 367 ($M-H$ for $C_{21}H_{20}O_6$).

Example 26B: Synthesis of 5-Methyl-4-(3'-trifluoromethyl-biphenyl-3-yloxymethyl)-furan-2-carboxylic acid (109)



Compound (**109**) was prepared from compound (**107**) and (3-trifluoromethyl-phenyl)-boronic acid by adapting the procedure of Example 26A(c). LC/MS System B; R_t = 1.97mins, m/z (ES^-) = 375 ($M-H$ for $C_{20}H_{15}F_3O_4$).

Example 27A: Synthesis of 4-(4'-Hydroxymethyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (110)



(i) 2-Chlorotrityl chloride resin (3.9 g of nominal loading 1.3 mmol/g) was swelled with dichloromethane (40 mL). After draining, a solution of 4-(4-iodo-phenoxy)-5-methyl-furan-2-carboxylic acid (**26**) (1.78g, 3.3mmoles) and diisopropylethylamine (2.3mL) in dichloromethane (30mL) was added and the mixture was shaken at room temperature for 72 hours. The resin was drained, washed sequentially with

dichloromethane/triethylamine/methanol (20:1:3 by volume) (3 x 30 mL), dichloromethane (6 x 30 mL), N,N-dimethylformamide (2 x 25 mL), dichloromethane (6 x 25 mL), and diethyl ether (2 x 25 mL) and dried at 40°C *in vacuo*.

5

(ii) The loaded resin (110mg) from (i) was treated with a mixture of (4-hydroxymethyl-phenyl)-boronic acid (98.3mg, 0.65mmoles), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (10.6mg) and cesium carbonate (0.212g, 0.65mmoles) in N,N-dimethylformamide (5mL) and the mixture was agitated at 40°C under a nitrogen atmosphere for 72 hours. The resin was drained, washed sequentially with tetrahydrofuran/water (1:1v/v) (2 x 5mL), tetrahydrofuran (2 x 5mL), N,N-dimethylformamide (3 x 5mL), dichloromethane (6 x 5mL) and diethyl ether (2 x 5mL), then dried at 45°C *in vacuo*.

10

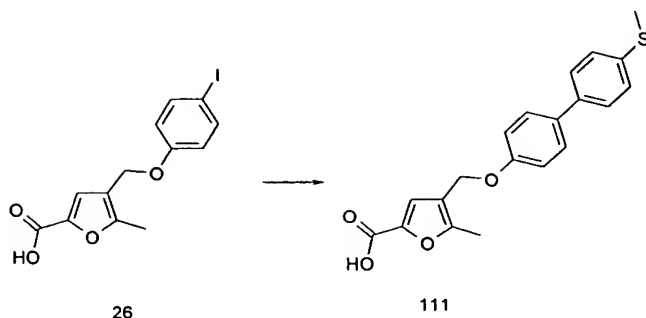
15

The resin was treated with dichloromethane/trifluoroacetic acid (19:1 by volume) (3mL) for 30 mins and the solution drained from the resin. This procedure was repeated. The combined solutions were concentrated *in vacuo* and the residue purified by hplc (gradient: 30% acetonitrile/70% water containing 0.1% trifluoroacetic acid to 90% acetonitrile/10% water at a rate of 1%/min) to compound **110** (18.3mg) as a solid. LC/MS System B; R_t = 1.48mins, m/z (ES^-) = 337 ($M-H$ for $C_{20}H_{18}O_5$).

20

25

Example 27B: Synthesis of 5-Methyl-4-(4'-methylsulphanyl-biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (111)

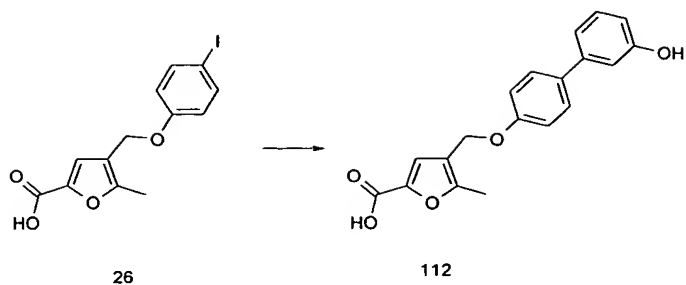


The loaded resin (110mg) (from example 27A, (i)) was treated with a mixture of (4-methylsulphonyl-phenyl)-boronic acid (109mg, 0.65mmoles), [1,1'-bis(diphenylphosphino)

5 ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (10.6mg) and potassium acetate (0.064g, 0.65mmoles) in N,N-dimethylformamide (5mL) and the mixture was agitated at 40°C for 60 hours. The resin was drained, washed sequentially with tetrahydrofuran/water (1:1v/v) (2 x 5mL),
10 tetrahydrofuran (2 x 5mL), N,N-dimethylformamide (3 x 5mL), dichloromethane (6 x 5mL) and diethyl ether (2 x 5ml), then dried at 45°C *in vacuo*.

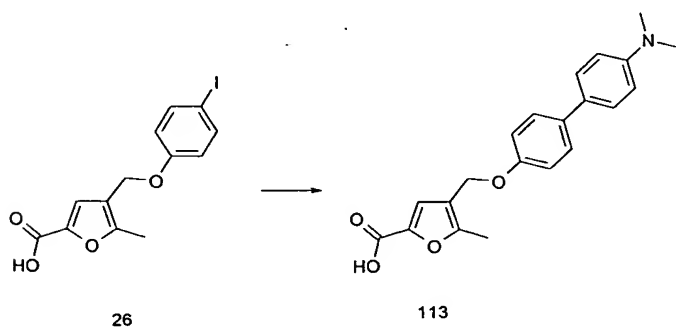
The resin was treated with dichloromethane/trifluoroacetic
15 acid (19:1 by volume) (3mL) for 30 mins and the solution drained from the resin. This procedure was repeated. The combined solutions were concentrated in *vacuo* and the residue purified by hplc (gradient: 30% acetonitrile/70% water containing 0.1% trifluoroacetic acid to 90%
20 acetonitrile/10% water at a rate of 1%/min) to afford compound **111** (5.0mg) as a solid. LC/MS System B; R_t = 1.90mins, m/z (ES^-) = 353 ($M-H$ for $C_{20}H_{18}O_4S$).

Example 27C: Synthesis of 4-(3'-Hydroxy-biphenyl-4-yloxy-methyl)-5-methyl-furan-2-carboxylic acid (112)
25



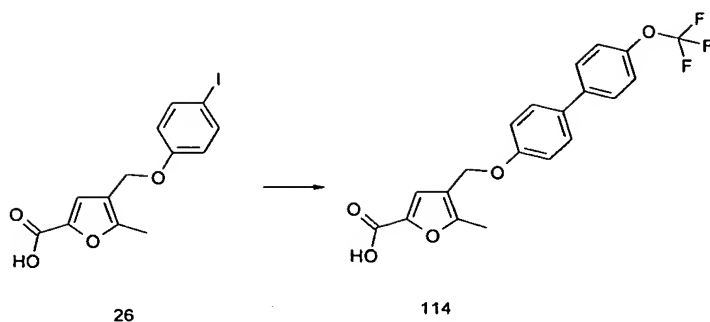
Compound (**112**) was prepared from compound (**26**) and (3-hydroxy-phenyl)-boronic acid by adapting the procedure of Example 27A. LC/MS System B; $R_t = 1.23$ mins, m/z (ES^-) = 323
5 (M-H for $C_{19}H_{16}O_5$).

Example 27D: 4-(4'-Dimethylamino-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (113)



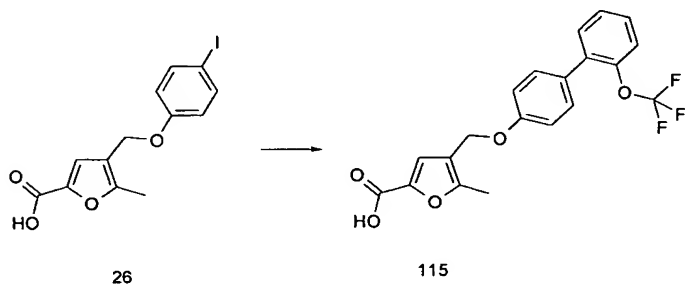
10 Compound (**113**) was prepared from compound (**26**) and (4-dimethylamino-phenyl)-boronic acid by adapting the procedure of Example 27B. LC/MS System B; $R_t = 1.83$ mins, m/z (ES^-) = 350 (M-H for $C_{21}H_{21}NO_4$).

15 **Example 27E: Synthesis of 5-Methyl-4-(4'-trifluoromethoxy-biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (114)**



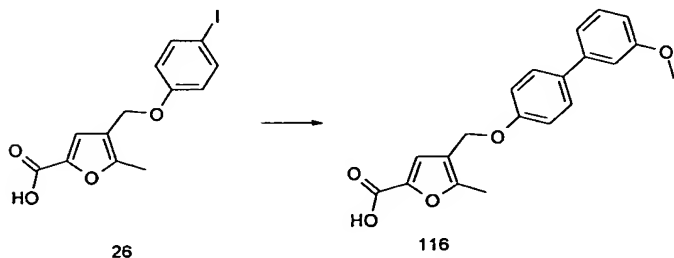
Compound (114) was prepared from compound (26) and (4-trifluoromethoxy-phenyl)-boronic acid by adapting the procedure of Example 27B. LC/MS System C; $R_t = 11.01$ mins,
5 m/z (ES^-) = 391 ($M-H$ for $C_{20}H_{15}F_3O_5$).

Example 27F: 5-Methyl-4-(2'-trifluoromethoxy-biphenyl-4-yloxymethyl)-furan-2-carboxylic acid (115)



10 Compound (115) was prepared from compound (26) and (2-trifluoromethoxy-phenyl)-boronic acid by adapting the procedure of Example 27B. LC/MS System B; $R_t = 1.97$ mins,
 m/z (ES^-) = 391 ($M-H$ for $C_{20}H_{15}F_3O_5$).

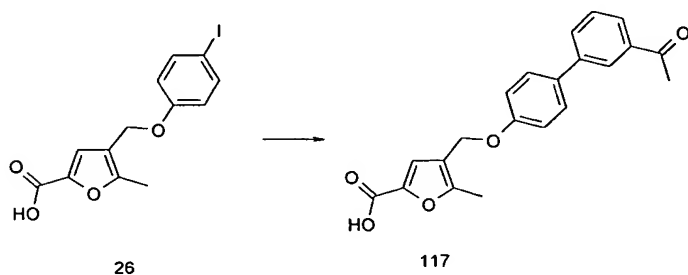
15 **Example 27G: Synthesis of 4-(3'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (116)**



Compound (116) was prepared from compound (26) and (3-

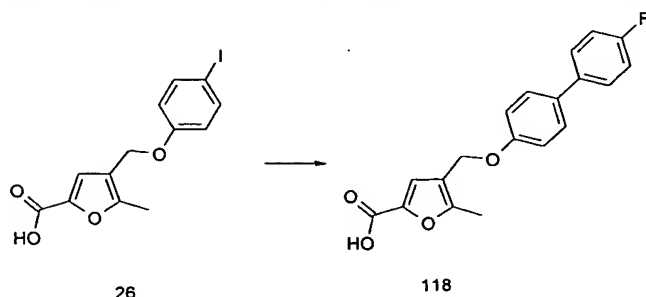
methoxy-phenyl)-boronic acid by adapting the procedure of Example 27B. LC/MS System B; $R_t = 1.79$ mins, m/z (ES^-) = 337 (M-H for $C_{20}H_{18}O_5$).

5 **Example 27H: Synthesis of 4-(3'-Acetyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (117)**



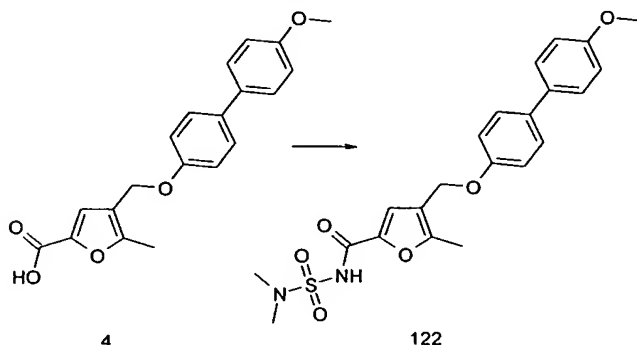
Compound (117) was prepared from compound (26) and (3-acetyl-phenyl)-boronic acid by adapting the procedure of Example 27B. LC/MS System B; $R_t = 1.69$ mins, m/z (ES^-) = 349 (M-H for $C_{21}H_{18}O_5$).

Example 27I: Synthesis of 4-(4'-Fluoro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (118)



Compound (118) was prepared from compound (26) and (4-fluoro-phenyl)-boronic acid by adapting the procedure of Example 27B. LC/MS System B; $R_t = 1.79$ mins, m/z (ES^-) = 325 (M-H for $C_{19}H_{15}FO_4$).

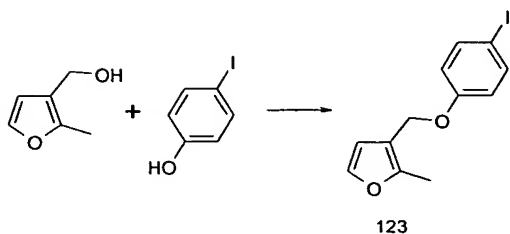
Example 28: Synthesis of N-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-dimethylamino-sulphonamide (122)



5 N,N-Dimethylsulphamide (73mg, 0.59mmoles), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (31mg, 0.162mmoles) and dimethyl-pyridin-4-yl-amine (1mg) were added to a stirred solution of 4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**) (50mg, 0.148mmoles) in dichloromethane (20ml). The mixture was stirred under an argon atmosphere for 18 hours. After evaporation of the solvent, the residue was partitioned between dichloromethane and water. The aqueous phase was separated and extracted with dichloromethane. The combined
10 extracts were washed with 1M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, brine and dried (MgSO₄). Evaporation of the solvent afforded the crude product, which was purified by HPLC (gradient: 30% acetonitrile/70% water containing 0.1% trifluoroacetic acid
15 to 98% acetonitrile/2% water at a rate of 1%/min) to afford compound **122** (23.5mg) as a white solid. LC/MS System C: R_t = 3.67 mins, m/z (ES⁻) = 443 ((M-H) for C₂₂H₂₄N₂O₆S).

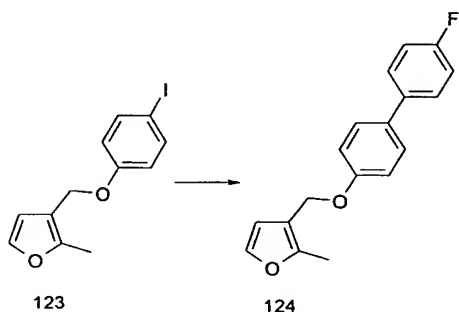
Example 29: Alternative synthesis of 4-(4'-Fluoro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (118)
25

(a) 3-(4-Iodo-phenoxyethyl)-2-methyl-furan (**123**)



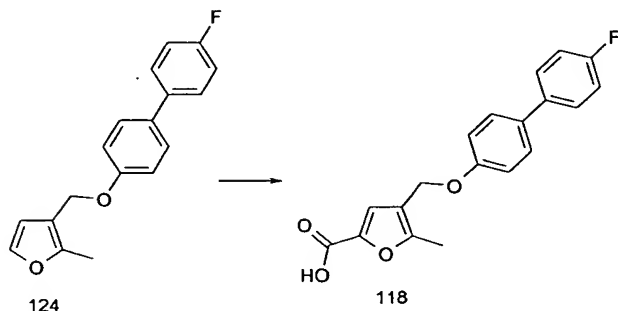
3-(4-Iodo-phenoxyethyl)-2-methyl-furan was prepared from (2-methyl-furan-3-yl)-methanol and 4-iodo-phenol in an analogous manner to that described in Example 14(a).

(b) 3-(4'-Fluoro-biphenyl-4-yloxyethyl)-2-methyl-furan (**124**)



A mixture of (4-fluoro-phenyl)-boronic acid (300mg, 2.1mmoles), 3-(4-iodophenoxyethyl)-2-methyl-furan (**123**) (500mg, 1.6mmoles) and potassium acetate (0.6g) in N,N-dimethylformamide (70mL) was degassed, treated with [1,1'-bis(diphenylphosphino) ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (90mg) and the mixture was agitated at 95°C for 12 hours under an argon atmosphere. The mixture was concentrated *in vacuo*, partitioned between water (100ml) and diethyl ether (200ml). The aqueous phase was re-extracted with diethyl ether, and the combined ethereal phases were dried and evaporated. The residue was purified by flash chromatography, using diethyl ether as eluent, to afford compound **124** (200mg) as a solid. This material was used directly.

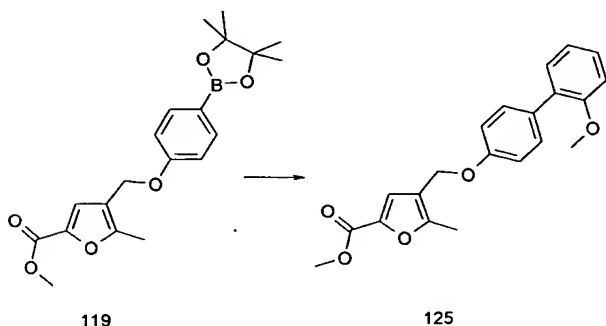
(c) 4-(4'-Fluoro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**118**)



A solution of 3-(4'-fluoro-biphenyl-4-yloxymethyl)-2-methyl-furan (**124**) (200mg, 0.71mmoles) in dry tetrahydrofuran (15ml) was cooled to -70°C and stirred under an argon atmosphere. The mixture was treated dropwise with *sec*-butyl lithium (0.6ml, of a 1.3M solution in cyclohexane) and stirred for 1 hour at -70°C. The reaction was quenched by the addition of excess solid carbon dioxide and allowed to warm to room temperature. The mixture was diluted with water, washed with diethyl ether and the aqueous phase acidified to pH = 6 with dilute aqueous hydrochloric acid. The mixture was extracted with ethyl acetate, the extracts dried (MgSO₄), and solvent removed *in vacuo* to give a yellow oil. The oil was purified by hplc to afford compound **118** (15mg) as a solid. LC/MS System A; R_t = 3.71mins, m/z (ES⁻) = 325 (M-H for C₁₉H₁₅FO₄).

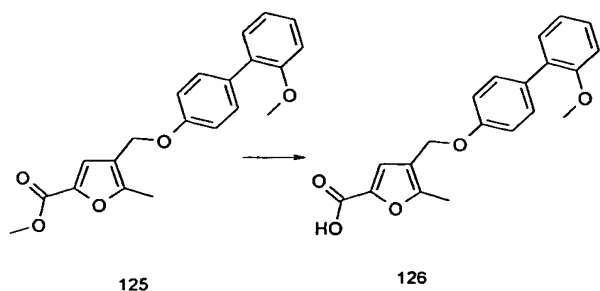
Example 30: Synthesis of 4-(2'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (126) and N-[4-(2'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (127)

(a) 4-(2'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**125**)



A degassed mixture of 5-methyl-4-[4-(4,4,5,5-tetramethyl-
5 [1,3,2]dioxaborolan-2-yl)-phenoxy]methyl-furan-2-carboxylic
acid methyl ester (**119**) (200mg, 0.54mmoles), 1-bromo-2-
methoxy-benzene (80 μ l, 0.65mmoles), 2M aqueous cesium
carbonate (1.0ml) and), [1,1'-bis(diphenylphosphino)
ferrocene]dichloropalladium(II) complex with dichloromethane
10 (1:1) (44mg) in 1,4-dioxan (30ml), under an argon atmosphere
was heated at 95°C for 18 hours. After cooling, the mixture
was concentrated, the residue dissolved in ethyl acetate and
washed with brine and dried. After evaporation of the
solvent, the residue was purified by flash chromatography
15 using cyclohexane/ethyl acetate 9:1v/v as eluent to afford
compound **125** (40mg) as an oil. LC/MS System A; R_t = 4.14
mins, m/z (ES^+) = 353weak ($M+H$ for $C_{21}H_{20}O_5$).

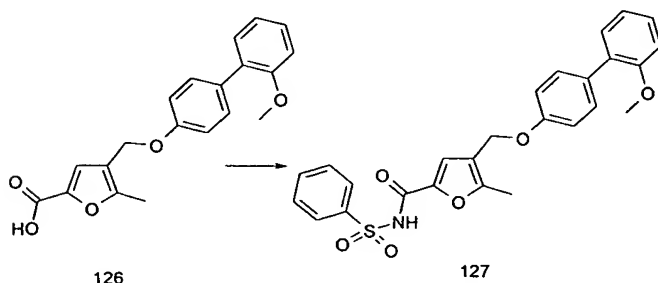
(b) 4-(2'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-
20 carboxylic acid (**126**)



A solution of 4-(2'-methoxy-biphenyl-4-yloxymethyl)-5-

methyl-furan-2-carboxylic acid methyl ester (**125**) (40mg, 0.11mmoles) in dry tetrahydrofuran (25ml) was treated with potassium trimethylsilanoate (73mg, 0.56mmoles) and the mixture stirred under an argon atmosphere for 16h. After
5 evaporation of the solvent the residue was acidified to pH = 2 with 0.1M aqueous hydrochloric acid and the mixture extracted with ethyl acetate. The dried extracts were evaporated and the residue pumped under high vacuum at 40°C to afford compound **126** (29mg) as an off-white solid. LC/MS
10 System D; R_t = 8.30mins, m/z (ES^+) = 339 ($M+H$ for $C_{20}H_{18}O_5$).

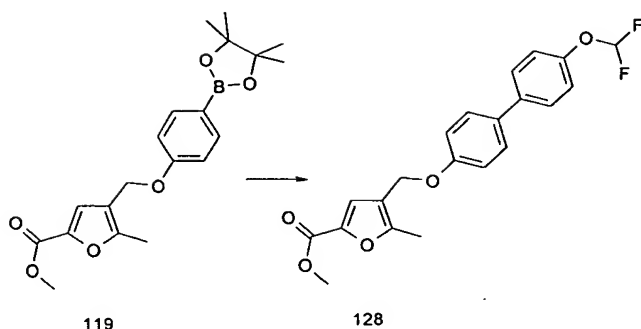
(c) *N*-[4-(2'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulphonamide (**127**)



15 Compound (**127**) was prepared from compound (**126**) by adapting the procedure of Example 2A. LC/MS System D; R_t = 9.17mins, m/z (ES^+) = 478 ($M+H$ for $C_{26}H_{23}NO_6S$).

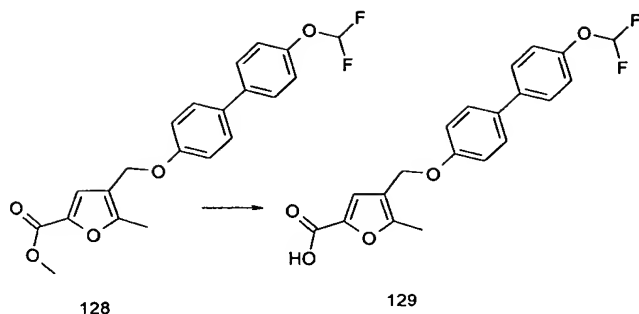
Example 31: Synthesis of 4-(4'-Difluoromethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (129**), *N*-[4-(4'-Difluoromethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (**130**) and 3,5-Dimethyl-isoxazole-4-sulfonic acid [4-(4'-difluoromethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (**131**)**

25 (a) 4-(4'-difluoromethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**128**)



A degassed mixture of 5-methyl-4-[4-(4,4,5,5-tetramethyl-
[1,3,2]dioxaborolan-2-yl)-phenoxy]methyl-furan-2-carboxylic
acid methyl ester (**119**) (200mg, 0.54mmoles), 4-
5 difluoromethoxy-1-iodo-benzene (175mg, 0.65mmoles), 2M
aqueous cesium carbonate (0.81ml) and), [1,1'-
bis(diphenylphosphino) ferrocene]dichloropalladium(II)
complex with dichloromethane (1:1) (20mg) in 1,4-dioxan
(10ml), under an argon atmosphere was heated at 80°C for
10 20h. Further quantities of 4-difluoromethoxy-1-iodo-benzene
(87.5mg, 0.0.27mmoles) and [1,1'-bis(diphenylphosphino)
ferrocene]dichloropalladium(II) complex with dichloromethane
(1:1) (10mg) were added and heating at 80°C was continued
for 4 hours. After cooling, the mixture was concentrated.
15 The residue was dissolved in dichloromethane and washed with
water and brine, and dried. The solvent was evaporated and
the residue was purified by flash chromatography using
petrol (40-60°)/diethyl ether 9:1v/v as eluent to afford
compound **128** (120mg) as a wax. LC/MS System A; R_t = 4.14
20 mins.

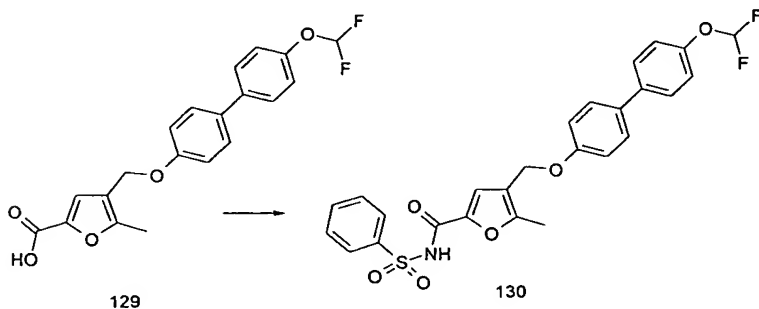
(b) 4-(4'-Difluoromethoxy-biphenyl-4-yloxy)methyl-5-methyl-
furan-2-carboxylic acid (**129**)



Compound (**129**) was prepared from compound (**128**) by adapting the procedure of Example 30(b). LC/MS System C; R_t = 8.53mins, m/z (ES^-) = 373 ($M-H$ for $C_{20}H_{16}F_2O_5$).

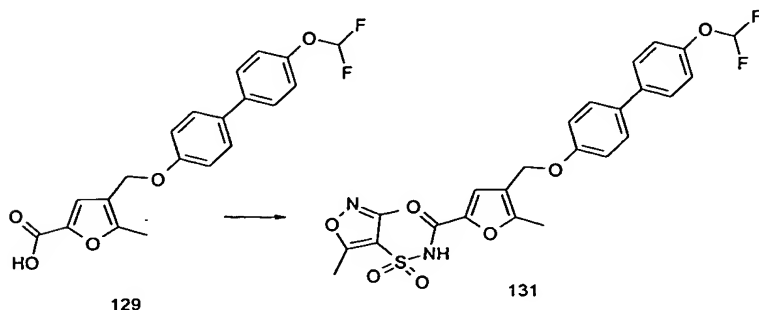
5

(c) *N*-[4-(4'-Difluoromethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulphonamide (**130**)



Compound (**130**) was prepared from compound (**129**) by adapting the procedure of Example 2A. LC/MS System C; R_t = 9.50mins, m/z (ES^-) = 512 ($M-H$ for $C_{26}H_{21}F_2NO_6S$).

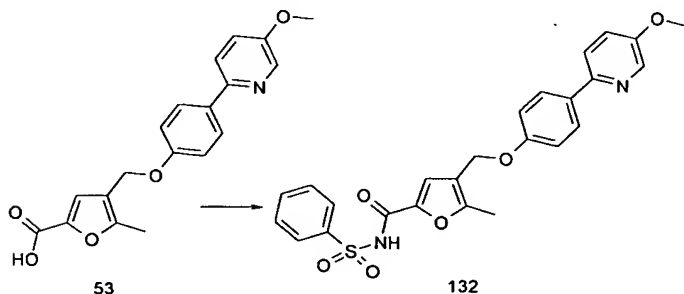
(d) 3,5-Dimethyl-isoxazole-4-sulphonic acid [4-(4'-difluoromethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (**131**)



Compound (131) was prepared from compound (129) by adapting the procedure of Example 2A. LC/MS System C; $R_t = 9.47$ mins, m/z (ES^-) = 531 ($M-H$ for $C_{25}H_{22}F_2N_2O_7S$).

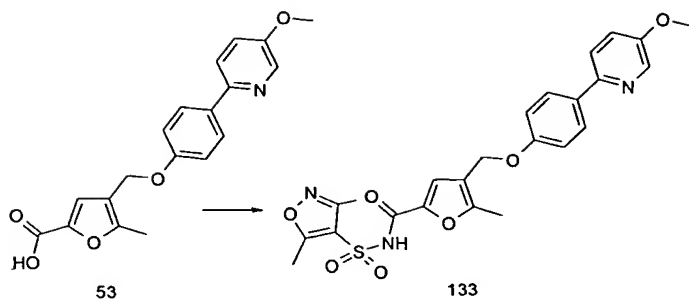
5 **Example 32: Synthesis of N-{4-[4-(5-Methoxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-2-carbonyl}-benzenesulfonamide (132), 3,5-Dimethyl-isoxazole-4-sulfonic acid {4-[4-(5-methoxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-2-carbonyl}-amide (133), N-{4-[4-(5-Methoxy-pyridin-2-yl)-**
10 **phenoxy-methyl]-5-methyl-furan-2-carbonyl}-2-methyl-benzenesulfonamide (134) and N-{4-[4-(5-Methoxy-1-oxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-2-carbonyl}-benzenesulfonamide (135)**

15 (a) N-{4-[4-(5-Methoxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-2-carbonyl}-benzenesulphonamide (132)



Compound (132) was prepared from compound (53) by adapting the procedure of Example 2A. LC/MS System D; $R_t = 7.10$ mins, m/z (ES^+) = 479 ($M+H$ for $C_{25}H_{22}N_2O_6S$).

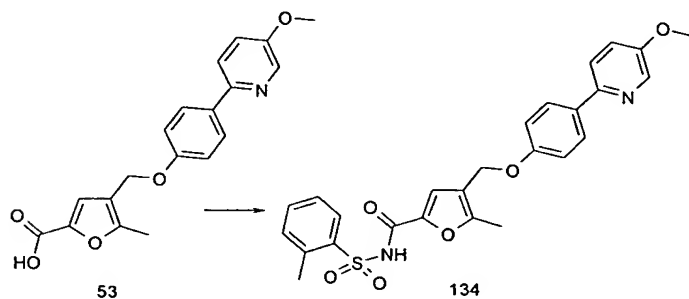
(b) 3,5-Dimethyl-isoxazole-4-sulphonic acid {4-[4-(5-methoxy-pyridin-2-yl)-phenoxy-methyl]-5-methyl-furan-2-carbonyl}-amide (133)



Compound (**133**) was prepared from compound (**53**) by adapting the procedure of Example 2A. LC/MS System D; $R_t = 7.83$ mins, m/z (ES^+) = 498 ($M+H$ for $C_{24}H_{23}N_3O_7S$).

5

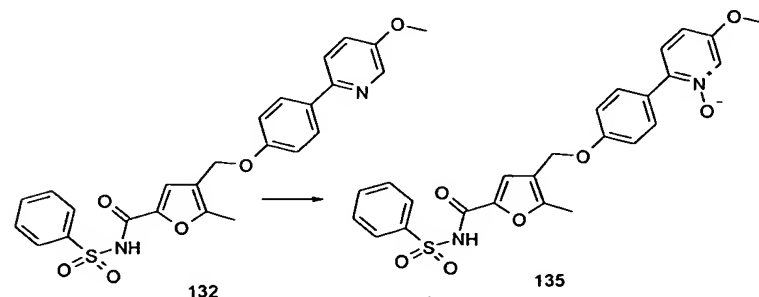
(c) *N*-(4-[4-(5-Methoxy-pyridin-2-yl)-phenoxy)methyl]-5-methyl-furan-2-carbonyl)-2-methyl-benzenesulphonamide (**134**)



Compound (**134**) was prepared from compound (**53**) by adapting the procedure of Example 2A. LC/MS System D; $R_t = 8.43$ mins, m/z (ES^+) = 493 ($M+H$ for $C_{26}H_{24}N_2O_6S$).

10

(d) *N*-(4-[4-(5-Methoxy-1-oxy-pyridin-2-yl)-phenoxy)methyl]-5-methyl-furan-2-carbonyl)-benzenesulphonamide (**135**)



15

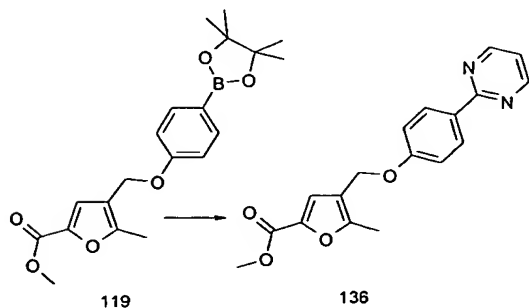
A solution of *N*-(4-[4-(5-methoxy-pyridin-2-yl)-phenoxy)methyl]-5-methyl-furan-2-carbonyl)-

benzenesulphonamide (**132**) (25mg, 0.042mmoles) in a mixture of methanol (0.5ml) and chloroform (1ml) was treated dropwise with a solution of 3-chloro-benzenecarboperoxoic acid (10.6mg of 72% wt.% peracid) in chloroform (1.5ml).

5 After stirring for 21 hours at room temperature, a further quantity of 3-chloro-benzenecarboperoxoic acid (8.0mg of 72% wt.% peracid) in chloroform (1ml) was added and the mixture stirred for 6 hours. Another aliquot of 3-chloro-benzenecarboperoxoic acid (8.0mg of 72% wt. % peracid) in
10 chloroform (1ml) was added and stirring continued for 21 hours. The mixture was evaporated and the residue was purified by HPLC (gradient: 25% acetonitrile/75% water containing 0.1% trifluoroacetic acid to 98% acetonitrile/2% water at a rate of 1%/min) to afford compound **135** (6mg) as a
15 solid. LC/MS System A; R_t = 3.03mins, m/z (ES^+) = 495 ($M+H$ for $C_{25}H_{22}N_2O_7S$).

Example 33: Synthesis of 5-Methyl-4-(4-pyrimidin-2-yl-phenoxy-methyl)-furan-2-carboxylic acid (137) and N-[5-Methyl-4-(4-pyrimidin-2-yl-phenoxy-methyl)-furan-2-carbonyl]-benzenesulfonamide (138)
20

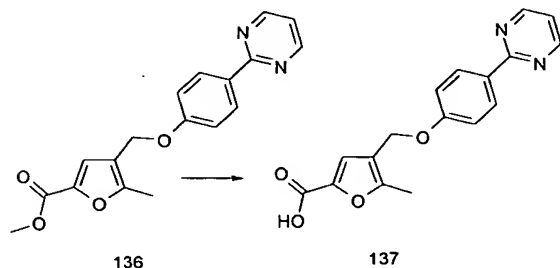
(a) 5-Methyl-4-(4-pyrimidin-2-yl-phenoxy-methyl)-furan-2-carboxylic acid methyl ester (**136**)



Compound (**136**) was prepared from compound (**119**) and 2-bromopyrimidine by adapting the procedure of Example 30(a). LC/MS System A; R_t = 3.43 mins, m/z (ES^+) = 325 ($M+H$ for

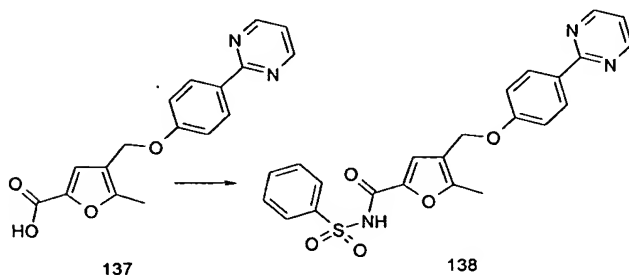
$C_{18}H_{16}N_2O_4$).

(b) 5-Methyl-4-(4-pyrimidin-2-yl-phenoxy-methyl)-furan-2-carboxylic acid (**137**)



Compound (**137**) was prepared from compound (**136**) by adapting the procedure of Example 30(b). LC/MS System D; R_t = 6.21mins, m/z (ES^+) = 311 ($M+H$ for $C_{17}H_{14}N_2O_4$).

10 (c) N-[5-Methyl-4-(4-pyrimidin-2-yl-phenoxy-methyl)-furan-2-carbonyl]-benzenesulphonamide (**138**)



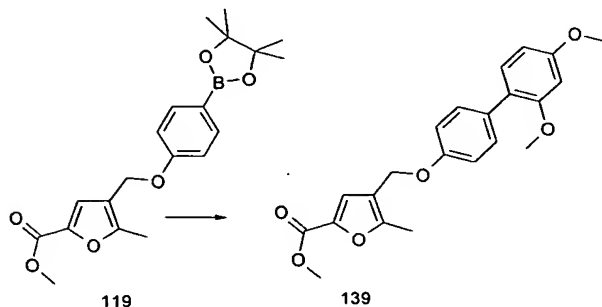
Compound (**138**) was prepared from compound (**137**) by adapting the procedure of Example 2A. LC/MS System D; R_t = 7.50mins, m/z (ES^+) = 450 ($M+H$ for $C_{23}H_{19}N_3O_5S$).

15

Example 34: Synthesis of 4-(2',4'-Dimethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (140), N-[4-(2',4'-Dimethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (141) and 3,5-Dimethyl-isoxazole-4-sulfonic acid [4-(2',4'-dimethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (142)

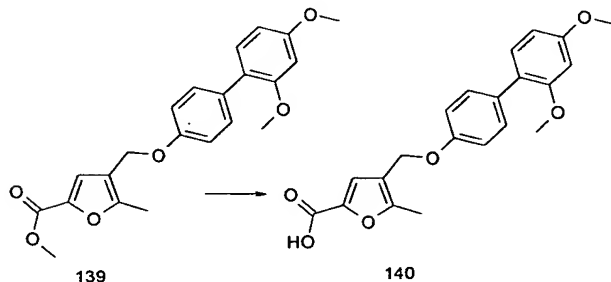
20

(a) 4-(2',4'-Dimethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**139**)



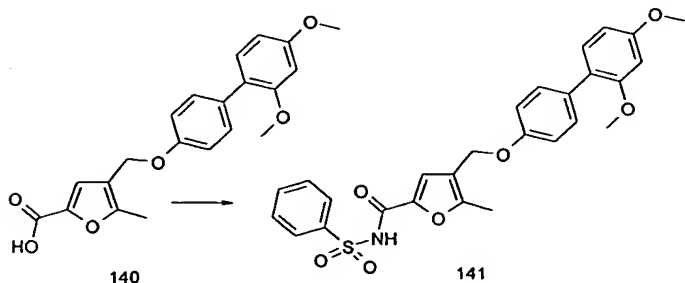
Compound (**139**) was prepared from compound (**119**) and 1-bromo-2,4-dimethoxybenzene by adapting the procedure of Example 31(a). LC/MS System A; $R_t = 4.09$ mins.

(b) 4-(2',4'-Dimethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**140**)



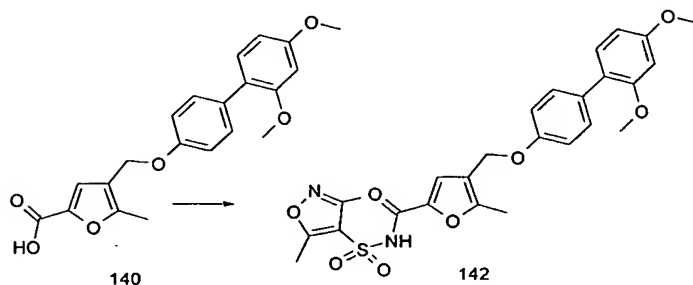
Compound (**140**) was prepared from compound (**139**) by adapting the procedure of Example 31(b). LC/MS System D; $R_t = 8.20$ mins, m/z (ES^+) = 369 ($M+H$ for $C_{21}H_{20}O_6$).

(c) N-[4-(2',4'-Dimethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulphonamide (**141**)



A stirred solution of 4-(2',4'-dimethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**140**) (50mg, 0.136mmoles), benzenesulphonamide (32mg, 0.204mmoles) and 4-(N,N-dimethylamino)-pyridine (5mg) in a mixture of tetrahydrofuran (8ml) and acetonitrile (2ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (32mg, 0.163mmoles). The mixture was stirred at room temperature for 16 hours under an argon atmosphere. The reaction mixture was concentrated in vacuo and the residue was purified by HPLC to afford compound **141** (24mg) as a white solid. LC/MS System C; R_t = 8.99mins, m/z (ES^-) = 506 (M-H for $C_{27}H_{25}NO_7S$).

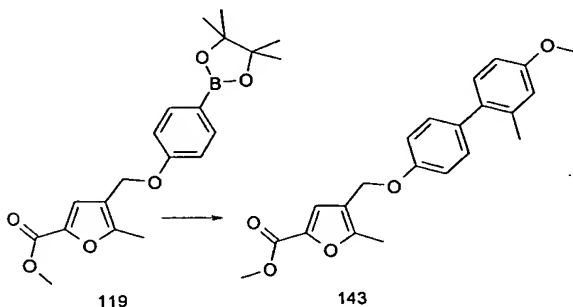
(d) 3,5-Dimethyl-isoxazole-4-sulphonic acid [4-(2',4'-dimethoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (**142**)



Compound (**142**) was prepared from compound (**140**) and 3,5-dimethyl-isoxazole-sulphonic acid amide by adapting the procedure of Example 34(c). LC/MS System C; R_t = 9.13mins, m/z (ES^-) = 525 (M-H for $C_{26}H_{26}N_2O_8S$).

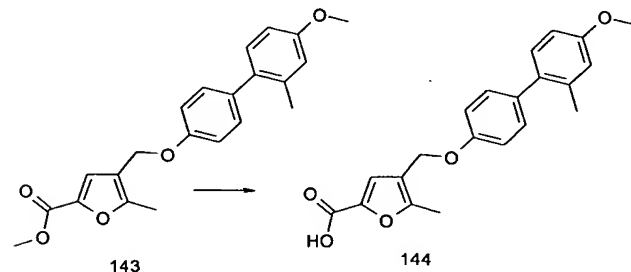
Example 35: Synthesis of 4-(4'-Methoxy-2'-methyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (144**), N-[4-(4'-Methoxy-2'-methyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (**145**) and 3,5-Dimethyl-isoxazole-4-sulfonic acid [4-(4'-methoxy-2'-methyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (**146**)**

(a) 4-(4'-Methoxy-2'-methyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**143**)



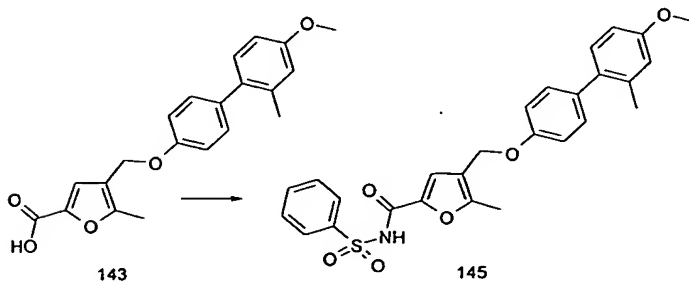
Compound (**143**) was prepared from compound (**119**) and 1-bromo-4-methoxy-2-methyl-benzene by adapting the procedure of Example 31(a). LC/MS System A; $R_t = 4.24$ mins.

(b) 4-(4'-Methoxy-2'-methyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**144**)



Compound (**144**) was prepared from compound (**143**) by adapting the procedure of Example 31(b). LC/MS System D; $R_t = 8.48$ mins, m/z (ES^+) = 353 ($M+H$ for $C_{21}H_{20}O_5$).

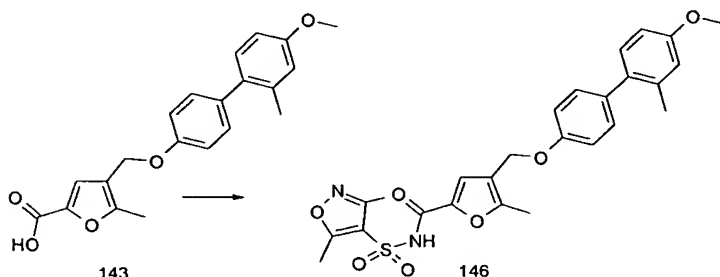
(c) N-[4-(4'-Methoxy-2'-methyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulphonamide (**145**)



Compound (**145**) was prepared from compound (**143**) and by

adapting the procedure of Example 34(c). LC/MS System C; R_t = 9.40mins, m/z (ES^-) = 490 ($M-H$ for $C_{27}H_{25}NO_6S$).

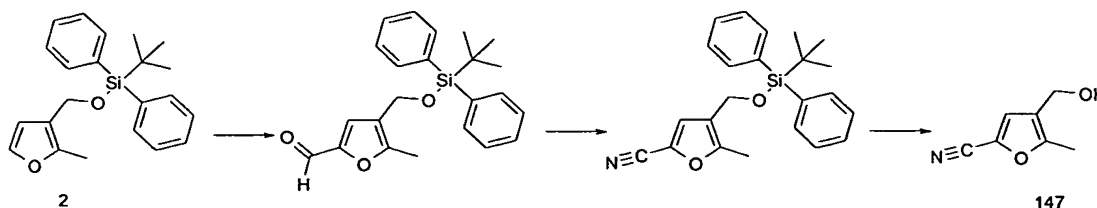
(d) 3,5-Dimethyl-isoxazole-4-sulphonic acid [4-(4'-methoxy-2'-methyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (**146**)



Compound (**146**) was prepared from compound (**143**) and 3,5-dimethyl-isoxazole-sulphonic acid amide by adapting the procedure of Example 34(c). LC/MS System D; R_t = 11.29mins, m/z (ES^-) = 509 ($M-H$ for $C_{26}H_{26}N_2O_7S$).

Example 36: Synthesis of 5-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-1H-tetrazole (149**)**

(a) 4-Hydroxymethyl-5-methyl-furan-2-carbonitrile (**147**)



(i) Sec-Butyl lithium (1.3M solution in cyclohexane, 57.1ml, 74.2mmoles) was added, dropwise during 10min, to a stirred solution of 4-(tert-butyl-diphenyl-silyloxymethyl)-5-methyl-furan (reference example 2A) (20.0g, 57.1mmoles) under an argon atmosphere and with cooling to -78°C . After stirring for an additional 45 minutes, the cooling bath was removed for 15 minutes, and then the reaction was re-cooled to -78°C . A solution of

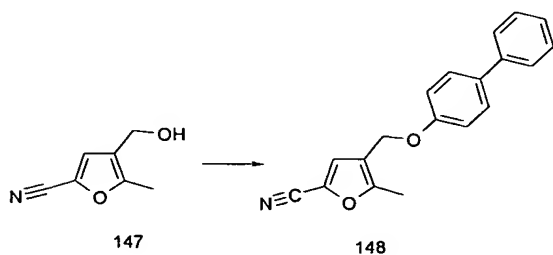
dimethylformamide (10ml) in tetrahydrofuran (40ml) was added during 5 minutes, the reaction mixture stirred for 2 hours at -78°C then allowed to warm to room temperature. The reaction was quenched by the addition of saturated aqueous ammonium chloride (200ml). Diethyl ether (500ml) was added the organic phase was separated, and the aqueous phase was extracted with diethyl ether (500ml). The combined extracts were washed with water (500ml) and brine (500ml), and dried (MgSO₄). Evaporation of the solvent afforded 4-(tert-butyl-diphenyl-silanyloxymethyl)-5-methyl-furan-2-carbaldehyde (20.4g).

(ii) Hydroxylamine hydrochloride (1.11g, 16.0mmoles) and triethylamine (2.22ml) were added to a solution of 4-(tert-butyl-diphenyl-silanyloxymethyl)-5-methyl-furan-2-carbaldehyde from (i) (6.3g, 16.0mmoles) in dichloromethane (125ml) and the mixture was stirred at room temperature for 17 hours. After cooling to 0°C, 2-Chloro-1,3-dimethylimidazolium chloride (2.81g, 16.6mmoles) and triethylamine (4.6ml) were added and the yellow suspension was stirred at room temperature for 24 hours. The mixture was diluted with water and extracted with dichloromethane. The combined extracts were washed with 5% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and water, and finally dried (MgSO₄). The solvent was evaporated and the residue was purified by flash chromatography (silica, cyclohexane/diethyl ether 99:1 v/v as eluent) to afford 4-(tert-butyl-diphenyl-silanyloxymethyl)-5-methyl-furan-2-carbonitrile as a viscous oil, (3.75g).

(iii) A solution of 4-(tert-butyl-diphenyl-silanyloxymethyl)-5-methyl-furan-2-carbonitrile from (ii) (3.75g) in tetrahydrofuran (100ml) was cooled to 0°C under

an argon atmosphere, and was treated with a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (22ml). The mixture was allowed to warm to room temperature and stirred for 16 hours. The volatiles were removed and the residue was partitioned between ethyl acetate and water. The organic phase was separated and the aqueous phase was extracted with more ethyl acetate. The combined ethyl acetate extracts were washed with 1M aqueous hydrochloric acid and brine, and dried. The solvent was evaporated and the crude orange oil was purified by flash chromatography (silica, gradient elution with 0% to 40% ethyl acetate in cyclohexane) to afford compound **147** as a pale yellow oil (1.3g).

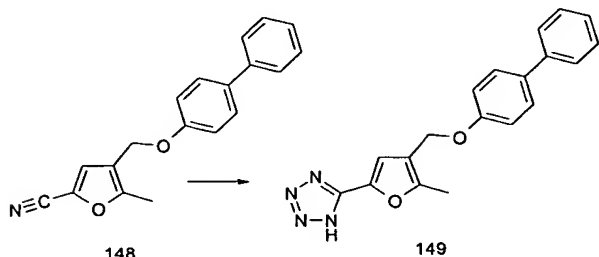
(b) 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonitrile (**148**)



Diisopropylazodicarboxylate (1.84g, 10.6mmoles) was added to a solution of 4-hydroxymethyl-5-methyl-furan-2-carbonitrile (**147**) (1.32g, 9.6mmoles), biphenyl-4-ol (1.63g, 9.6mmoles) and triphenylphosphine (4.3g, 16.35mmoles) in tetrahydrofuran (50mL) with stirring and cooling to 0°C under an argon atmosphere. After 5 minutes, the cooling was removed and the mixture stirred at room temperature for 16h. The solvent was evaporated and the residue partitioned between ethyl acetate and water. The ethyl acetate phase was washed with brine and dried. After the solvent was evaporated, the residue was purified by flash chromatography (silica, gradient elution with 5% to 10% ethyl acetate in cyclohexane) to afford compound **148** as a white solid (2.2g).

IR (powder) CN st. 2225cm^{-1} .

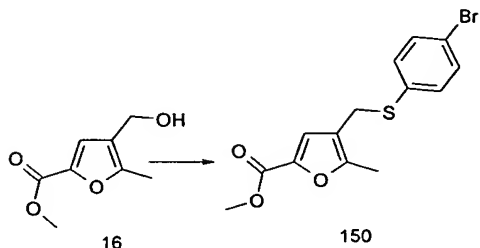
(c) 5-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-1H-tetrazole (**149**)



A mixture of 4-(biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonitrile (**148**) (100mg, 0.35mmoles), sodium azide (27mg, 0.415mmoles) and potassium carbonate (62mg, 0.45mmoles) in dimethylformamide (5ml) was heated at 90°C for 96 hours then
10 at 120°C for 24 hours. The mixture was evaporated and the residue purified by HPLC to afford compound **149** as a white solid (64mg). LC/MS System D; $R_t = 9.53\text{mins}$, m/z (ES^+) = 333 ($\text{M}+\text{H}$ for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_2$).

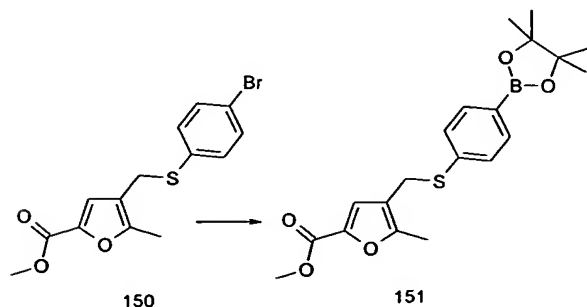
15 **Example 37: Synthesis of 4-(4'-Difluoromethoxy-biphenyl-4-ylsulfanylmethyl)-5-methyl-furan-2-carboxylic acid (153), N-[4-(4'-Difluoromethoxy-biphenyl-4-ylsulfanylmethyl)-5-methyl-furan-2-carbonyl]-2-methyl-benzenesulfonamide (154),**
20 **N-[4-(4'-Difluoromethoxy-biphenyl-4-ylsulfanylmethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (155) and N-[4-(4'-Difluoromethoxy-biphenyl-4-sulfinylmethyl)-5-methyl-furan-2-carbonyl]-2-methyl-benzenesulfonamide (156)**

(a) 4-(4-Bromo-phenylsulphanylmethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**150**)



Diisopropylazodicarboxylate (1.27g, 6.3mmoles) was added to
5 a solution of triphenylphosphine (1.65g, 6.3mmoles) in
tetrahydrofuran (15ml) with stirring and cooling in an
ice/water bath. A solution of 4-hydroxymethyl-5-methyl-
furan-2-carboxylic acid methyl ester (**16**) (536mg,
3.15mmoles) and 4-bromo-thiophenol (584mg, 3.09mmoles) in
10 tetrahydrofuran (5ml) was added and the mixture stirred for
30 minutes at 0°C then 72 hours at room temperature. The
solvent was evaporated and the residue extracted with
heptane then diethyl ether. The extracts were combined and
evaporated to give a yellow oil which was purified by by
15 flash chromatography using heptane/ethyl acetate 9:1v/v as
eluent. This gave compound **150** (600mg) as a white solid.
LC/MS System A; R_t = 4.12mins.

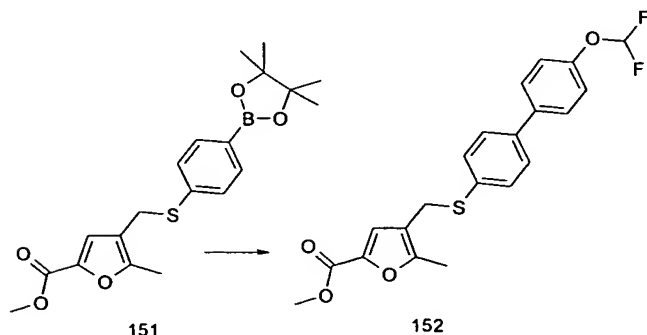
(b) 5-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-
2-yl)-phenylsulphanylmethyl]-furan-2-carboxylic acid methyl
20 ester (**151**)



[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)

complex with dichloromethane (1:1) (30mg) and 4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2.34ml of a 1M solution in tetrahydrofuran) were added to a degassed solution of 4-(4-bromo-phenylsulphanylmethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**150**) (400mg, 1.17mmoles) in 1,4-dioxan (120ml). The mixture was heated at 100°C, under an argon atmosphere, for 20 hours, cooled and evaporated. The residue was partitioned between ethyl acetate and water, and the organic phase washed with brine and dried (MgSO₄). After evaporation of the solvent the residue was purified by by flash chromatography, using heptane/ethyl acetate 9:1v/v as eluent, to afford compound **151** (212mg) as a colourless oil.

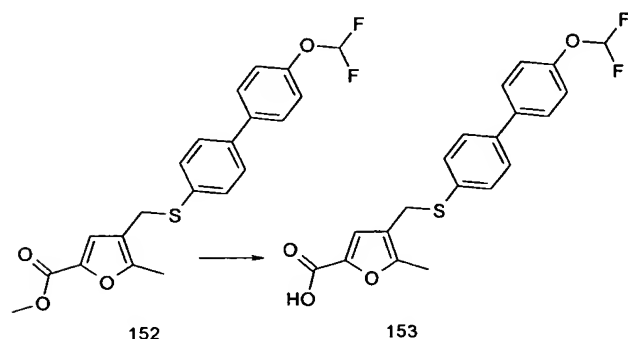
(c) 4-(4'-difluoromethoxy-biphenyl-4-ylsulphanylmethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**152**)



[1,1'-Bis(diphenylphosphino) ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (12.8mg) was added to a degassed mixture of 5-methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylsulphanylmethyl]-furan-2-carboxylic acid methyl ester (**151**) (200mg, 0.516mmoles), 1-difluoromethoxy-4-iodo-benzene (153mg, 0.568mmoles) and 2M aqueous cesium carbonate (4.12ml) in 1,4-dioxan (15ml). The mixture was placed under an argon atmosphere and was heated at 100°C for 20 hours. After cooling, the mixture was concentrated and the residue was partitioned between ethyl acetate and water, and the mixture adjusted to pH= 2 with 1M

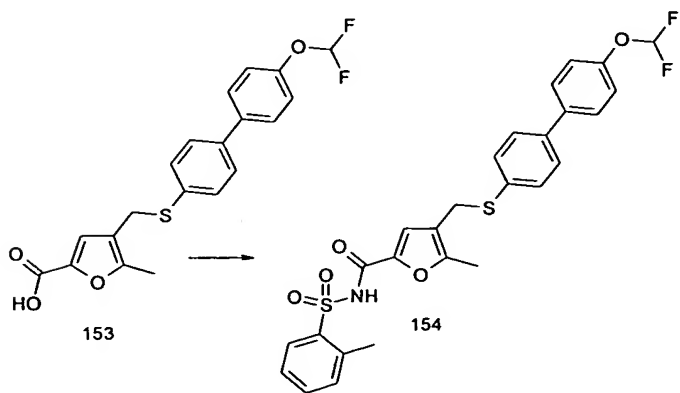
aqueous hydrochloric acid. The organic phase was washed with brine and dried. After evaporation of the solvent, the residue was purified by flash chromatography, using heptane/ethyl acetate 9:1v/v as eluent, to afford compound
5 **152** (126mg) as a white solid. LC/MS System A; R_t = 4.17mins.

(d) 4-(4'-Difluoromethoxy-biphenyl-4-ylsulphanylmethyl)-5-methyl-furan-2-carboxylic acid (**153**)



10 Compound (**153**) was prepared from compound (**152**) by adapting the procedure of Example 30(b) (127mg) as a white solid. LC/MS System D; R_t = 10.34mins, m/z (ES^-) = 389 ($M-H$ for $C_{20}H_{16}F_2O_4S$).

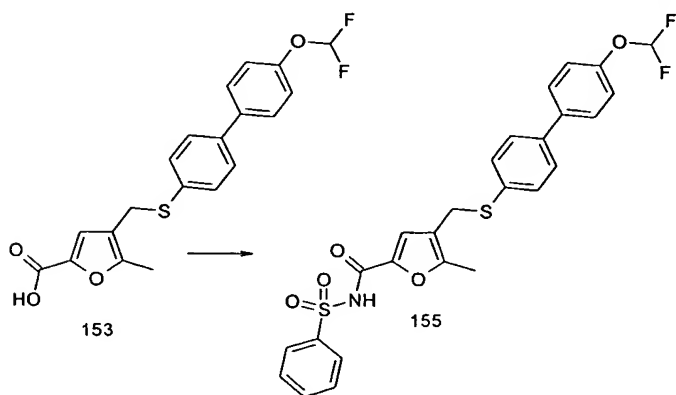
15 (e) *N*-[4-(4'-Difluoromethoxy-biphenyl-4-ylsulphanylmethyl)-5-methyl-furan-2-carbonyl]-2-methyl-benzenesulphonamide (**154**)



Compound (**154**) was prepared from compound (**153**) and 2-methyl-benzenesulphonamide by adapting the procedure of
20

Example 34(c). LC/MS System D; $R_t = 11.61\text{mins}$, m/z (ES^+) = 544 ($\text{M}+\text{H}$ for $\text{C}_{27}\text{H}_{23}\text{F}_2\text{NO}_5\text{S}_2$).

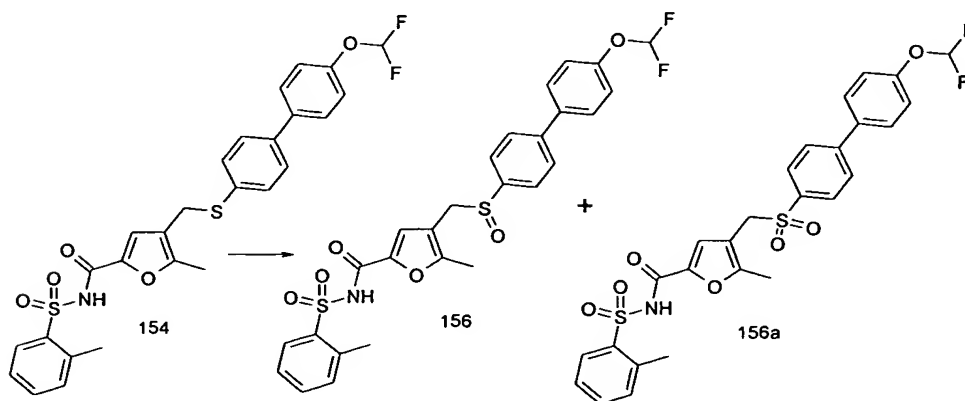
(f) *N*-[4-(4'-difluoromethoxy-biphenyl-4-ylsulphanylmethyl)-5-methyl-furan-2-carbonyl]-benzenesulphonamide (**155**)



Compound (**155**) was prepared from compound (**153**) by adapting the procedure of Example 2A. LC/MS System D; $R_t = 11.44\text{mins}$, m/z (ES^+) = 530 ($\text{M}+\text{H}$ for $\text{C}_{26}\text{H}_{21}\text{F}_2\text{NO}_5\text{S}_2$).

10

(g) *N*-[4-(4'-difluoromethoxy-biphenyl-4-ylsulphanylmethyl)-5-methyl-furan-2-carbonyl]-2-methyl-benzenesulphonamide (**156**) and *N*-[4-(4'-difluoromethoxy-biphenyl-4-sulfonylmethyl)-5-methyl-furan-2-carbonyl]-2-methyl-benzenesulfonamide (**156a**)



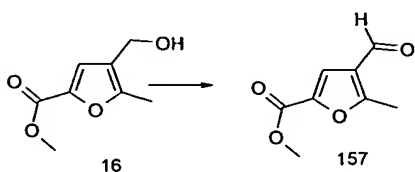
A solution of 3-chloro-benzenecarboxylic acid (22mg of 72% wt peracid) in chloroform (3ml) was added to a solution of *N*-[4-(4'-difluoromethoxy-biphenyl-4-ylsulphanylmethyl)-5-

methyl-furan-2-carbonyl]-2-methyl-benzenesulphonamide (**154**) (50mg, 0.092mmoles) in a mixture of methanol (1ml) and chloroform (2ml). After stirring for 2 hours, the solvent was evaporated and the residue was purified by HPLC (gradient: 45% acetonitrile/55% water containing 0.1% trifluoroacetic acid to 98% acetonitrile/2% water at a rate of 1%/min) to afford compound **156** (42mg) as a white solid. LC/MS System D; R_t = 9.61mins, m/z (ES^-) = 558 ($M-H$ for $C_{27}H_{23}F_2NO_6S_2$).

Also obtained was N-[4-(4'-difluoromethoxy-biphenyl-4-ylsulphonylmethyl)-5-methyl-furan-2-carbonyl]-2-methyl-benzenesulphonamide (**156a**) (8mg) as a white solid. LC/MS System D; R_t = 10.24mins, m/z (ES^-) = 574 ($M-H$ for $C_{27}H_{23}F_2NO_7S_2$).

Example 38: Synthesis of 4-(Biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carboxylic acid (160), N-[4-(Biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (161) and N-[4-(Biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carbonyl]-2-methyl-benzenesulfonamide (162)

(a) 4-Formyl-5-methyl-furan-2-carboxylic acid methyl ester (**157**)

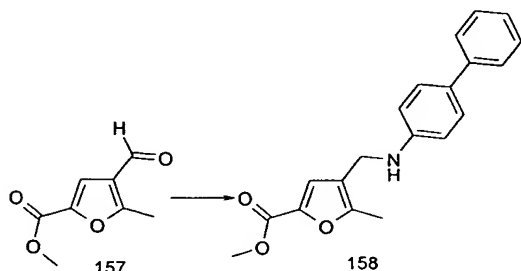


Acetic acid 1,1-diacetoxy-3-oxo-1^λ5-ioda-2-oxa-indan-1-yl

ester (Dess-Martin reagent) (549mg, 1.293mmoles) in dry dichloromethane was added to a solution of 4-hydroxymethyl-5-methyl-furan-2-carboxylic acid methyl ester (**16**) (200mg, 1.176mmoles) in dry dichloromethane (9ml) with cooling to 0°C under an argon atmosphere. After stirring for 20 minutes, the mixture was diluted with diethyl ether (40ml) and was poured into saturated aqueous sodium bicarbonate

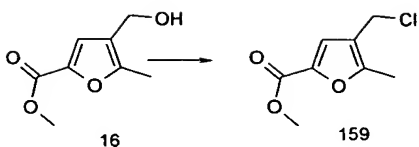
(30ml) containing sodium thiosulphate pentahydrate (4g) and agitated vigorously for 5 minutes. The organic phase was washed with saturated aqueous sodium bicarbonate (40ml), water (50ml) and brine (50ml) and dried. After removal of the solvent, the residue was purified by flash chromatography, using petrol/diethyl ether 4:1 v/v as eluent, to afford compound **157** (140mg) as a white solid.

(b) 4-(Biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**158**)



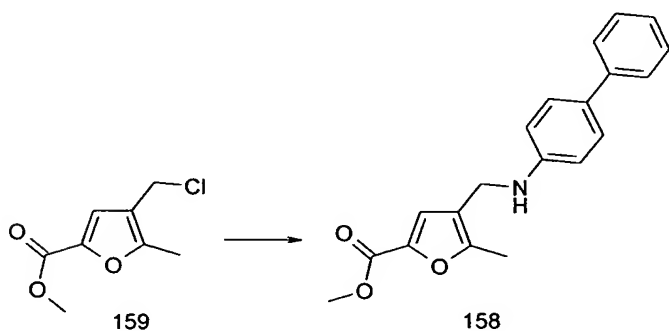
A solution of biphenyl-4-ylamine (150mg, 0.883mmoles) and 4-formyl-5-methyl-furan-2-carboxylic acid methyl ester (**157**) (135mg, 0.803mmoles) in methanol (2.0ml) was stirred over molecular sieves (type 3Å) for 1hour. Sodium cyanoborohydride (55mg, 0.883mmoles) was added and the mixture stirred for 18 hour at room temperature. The mixture was concentrated and partitioned between ethyl acetate (25ml) and saturated aqueous sodium bicarbonate (30ml). The aqueous phase was re-extracted with ethyl acetate (2 x 25ml) and the combined extracts were washed with brine (50ml) and dried (MgSO₄). After removal of the solvent, the residue was purified by by flash chromatography, using a gradient elution of petrol/diethyl ether 9:1 v/v to 4:1 v/v, to afford compound **158** (75mg).

(c) 4-Chloromethyl-5-methyl-furan-2-carboxylic acid methyl ester (**159**)



Triethylamine (196 μ l, 1.41mmoles), followed by 4-methyl-benzenesulphonyl chloride (247mg, 1.293mmoles) were added to a stirred solution of 4-hydroxymethyl-5-methyl-furan-2-carboxylic acid methyl ester (**16**) (200mg, 1.176mmoles) in dry dichloromethane at 0°C under an argon atmosphere. The reaction mixture was stirred at 0°C for 15 minutes, then allowed to warm to room temperature and was stirred for a further 4 hours. The mixture was washed with saturated aqueous sodium bicarbonate (50ml) and brine (50ml), and dried (MgSO₄). After removal of the solvent, the residue was purified by flash chromatography, using petrol/diethyl ether 19:1 v/v as eluent, to afford compound **159** (75mg) as a white solid. LC/MS System D; R_t = 6.34 mins, m/z (ES⁺) = 189 (M+H for C₈H₉ClO₃).

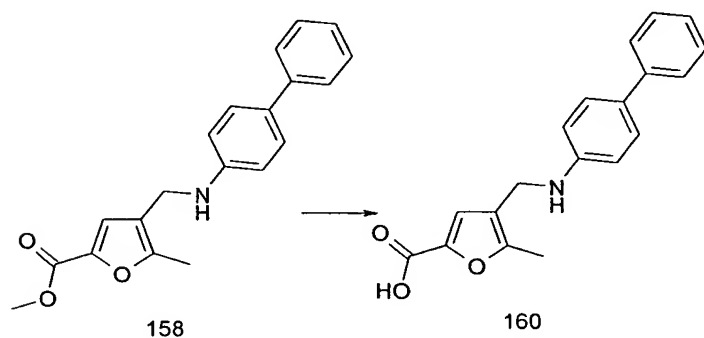
(d) 4-(Biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**158**)



Potassium iodide (32mg) and a solution of biphenyl-4-ylamine (74mg, 0.438mmoles) in tetrahydrofuran (1ml) was added to a mixture of 4-chloromethyl-5-methyl-furan-2-carboxylic acid methyl ester (**159**) (75mg, 0.398mmoles) and potassium carbonate (83mg) in tetrahydrofuran (1ml). The mixture was stirred at room temperature under an argon atmosphere for 16

hours, and then refluxed with the exclusion of light for 16 hours. After cooling, the mixture was concentrated and the residue was purified by by flash chromatography, using a gradient elution of petrol/diethyl ether 9:1 v/v to 4:1 v/v, to afford compound **158** (91mg). LC/MS System A; R_t = 3.93 mins, m/z (ES^+) = 322 ($M+H$ for $C_{20}H_{19}NO_3$).

(e) 4-(Biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carboxylic acid (**160**)

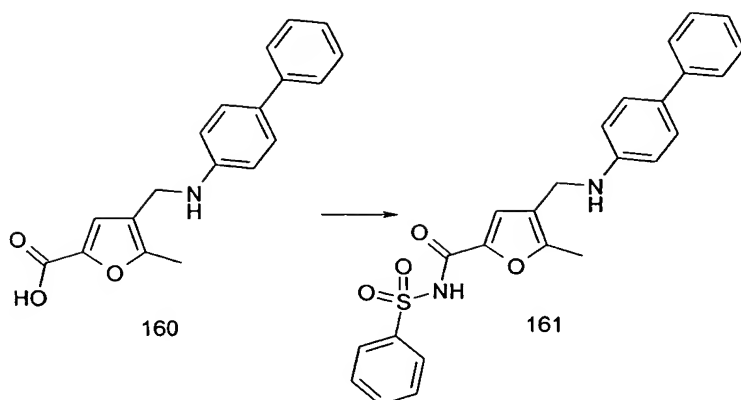


A solution of 4-(biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**158**) (91mg, 0.283mmoles) in dry tetrahydrofuran (5ml) was treated with potassium trimethylsilanoate (182mg, 1.42mmoles) and the mixture stirred under an argon atmosphere for 3 hours. After evaporation of the solvent, the residue was purified by HPLC (gradient: 15% acetonitrile/85% water containing 0.1% trifluoroacetic acid to 55% acetonitrile/45% water at a rate of 1%/min) to afford compound **160** (35mg) as a white solid. LC/MS System D; R_t = 7.64mins, m/z (ES^+) = 308 ($M+H$ for $C_{19}H_{17}NO_3$).

15

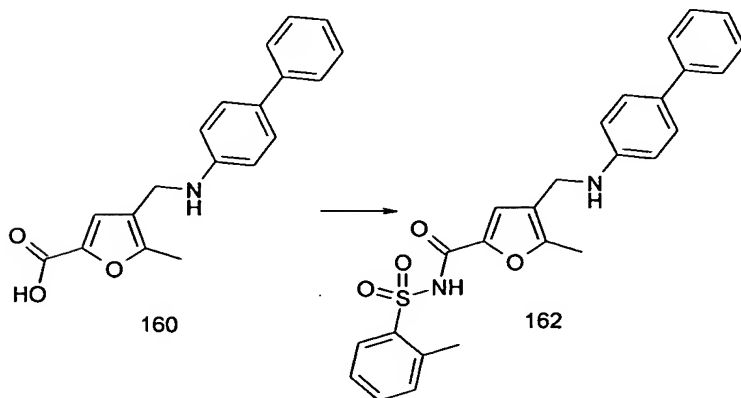
20

(f) N-[4-(biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carbonyl]-benzenesulphonamide (**161**)



A stirred solution of 4-(biphenyl-4-ylaminomethyl)-5-methylfuran-2-carboxylic acid (**160**) (15mg, 0.036mmoles), benzenesulphonamide (17mg, 0.107mmoles) and 4-(N,N-dimethylamino)-pyridine (1mg) in a mixture of tetrahydrofuran (3ml) and acetonitrile (0.5ml) was treated with triethylamine (5.5μl, 0.039mmoles) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (10.5mg, 0.053mmoles). The mixture was stirred at room temperature for 19 hours under an argon atmosphere. The reaction mixture was concentrated *in vacuo* and the residue was purified by HPLC to afford compound **161** (8mg) as a white solid. LC/MS System D; R_t = 8.84mins, m/z (ES^+) = 447 ($M+H$ for $C_{25}H_{22}N_2O_4S$).

(g) *N*-[4-(biphenyl-4-ylaminomethyl)-5-methylfuran-2-carbonyl]-2-methylbenzenesulphonamide (**162**)

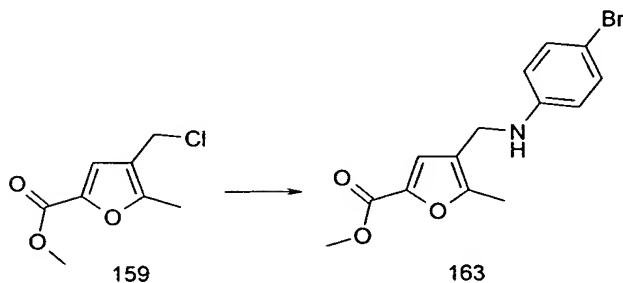


Compound (**162**) was prepared from compound (**160**) and 2-methyl-benzenesulphonamide by adapting the procedure of Example 38(f). LC/MS System D; $R_t = 10.39$ mins, m/z (ES^+) = 461 ($M+H$ for $C_{26}H_{24}N_2O_4S$).

5

Example 39: Synthesis of N-(4-{[4-(5-Methoxy-pyridin-2-yl)-phenylamino]-methyl}-5-methyl-furan-2-carbonyl)-2-methyl-benzenesulfonamide (167**)**

10 (a) 4-[(4-Bromo-phenylamino)-methyl]-5-methyl-furan-2-carboxylic acid methyl ester (**163**)



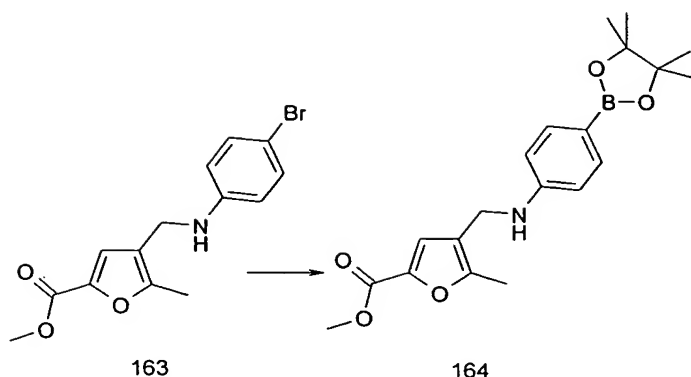
A mixture of 4-chloromethyl-5-methyl-furan-2-carboxylic acid methyl ester (**159**) (0.5g, 2.65mmoles), 4-bromoaniline

15 (2.28g, 13.25mmoles) and potassium carbonate (0.55g, 3.98mmoles) in tetrahydrofuran (25ml) was stirred at gentle reflux for 72 hours. The mixture was evaporated to give a yellow residue, which was purified by HPLC to afford compound **163** as a trifluoroacetic acid salt (840mg). LC/MS

20 System A; $R_t = 3.82$ mins, m/z (ES^+) = 324/326 ($M+H$ for $C_{14}H_{14}BrNO_3$).

(b) 5-Methyl-4-[[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamino]-methyl-furan-2-carboxylic acid methyl ester (**164**)

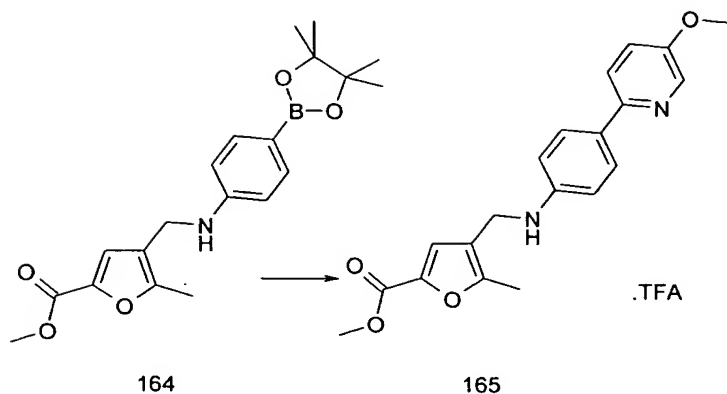
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A mixture of 4-[(4-bromo-phenylamino)-methyl]-5-methyl-furan-2-carboxylic acid methyl ester (**163**) (280mg,

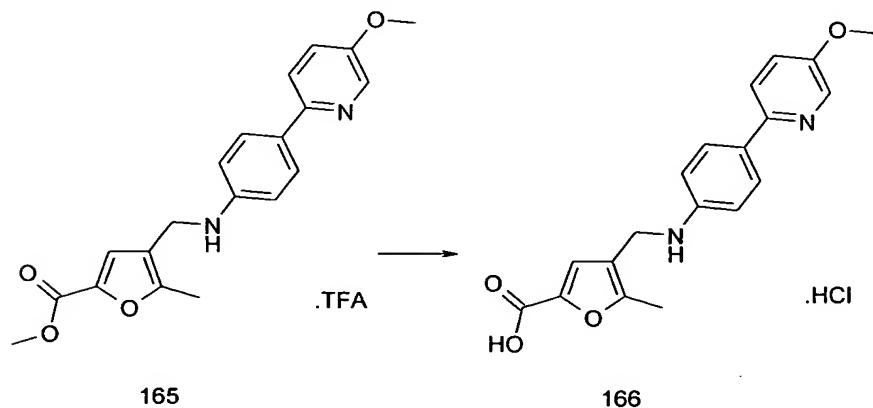
5 0.864mmoles), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (21mg), 4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (240mg, 0.950mmoles) and potassium acetate (250mg, 2.59mmoles) in dimethyl sulphoxide (6ml) was degassed and
10 placed under an argon atmosphere. The mixture was heated at 80°C for 5 hours, cooled and toluene (100ml) was added. The mixture was washed with water (50ml) and sodium bicarbonate was added until the pH =9. The aqueous phase was discarded and the toluene layer filtered. After evaporation of the
15 solvent the residue was purified by flash chromatography (silica, heptane/ethyl acetate 4:1v/v as eluent) to give compound **164** as an oil, which was used directly in the next step.

20 (c) 4-{[4-(5-Methoxy-pyridin-2-yl)-phenylamino]-methyl}-5-methyl-furan-2-carboxylic acid methyl ester trifluoroacetic acid salt (**165**)



5-Methyl-4-([4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamino]-methyl-furan-2-carboxylic acid methyl ester (**164**) (130mg, 0.525mmoles) was added to a degassed mixture of 2-bromo-5-methoxy-pyridine (99mg, 0.350mmoles), bis(dibenzylidene-acetone)-palladium(0) (6mg) and triphenyl-phosphine (11mg) in toluene/dimethylformamide 1:1 v/v (5ml) under an argon atmosphere. Aqueous potassium carbonate (0.23ml of a 3M solution) was added and the mixture was heated at 100°C for 16 hours. The reaction mixture was concentrated and the residue was purified by HPLC to afford compound **165** (38mg). LC/MS System A; $R_t = 2.55$ mins, m/z (ES^+) = 353 ($M+H$ for $C_{20}H_{20}N_2O_4$).

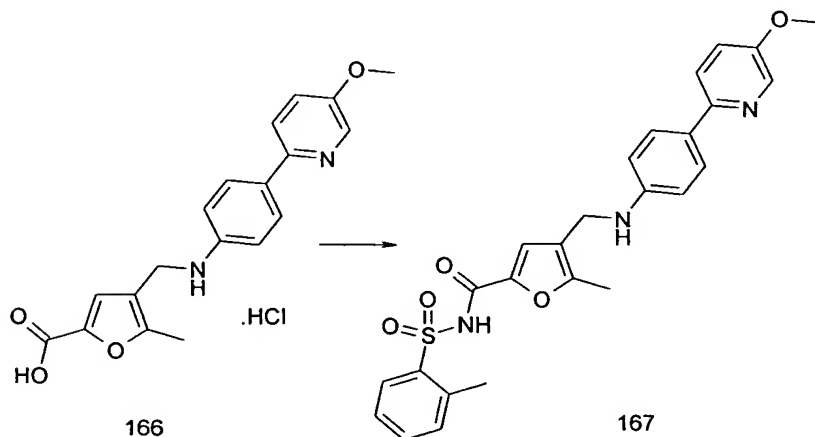
(d) 4-([4-(5-Methoxy-pyridin-2-yl)-phenylamino]-methyl)-5-methyl-furan-2-carboxylic acid hydrochloride salt (**166**)



A solution of 4-([4-(5-methoxy-pyridin-2-yl)-phenylamino]-

methyl}-5-methyl-furan-2-carboxylic acid methyl ester
trifluoroacetic acid salt (**165**) (38mg, 0.082mmoles) in
tetrahydrofuran (4ml) was treated with potassium
trimethylsilanoate (63mg, 0.049mmoles) and the mixture
5 stirred at room temperature for 16 hours. The mixture was
evaporated to dryness and pumped under high vacuum to remove
silanol volatiles. The residue was purified by HPLC to
afford a residue, which was dissolved in 1M aqueous
hydrochloric acid. The solution was evaporated to give
10 compound **166** as a solid (30mg). LC/MS System A; R_t =
2.22mins, m/z (ES^+) = 339 ($M+H$ for $C_{19}H_{18}N_2O_4$) and m/z (ES^-) =
337 ($M-H$ for $C_{26}H_{25}N_3O_5S$).

(e) *N*-(4-([4-(5-Methoxy-pyridin-2-yl)-phenylamino]-methyl)-
15 5-methyl-furan-2-carbonyl)-2-methyl-benzenesulphonamide
(**167**)

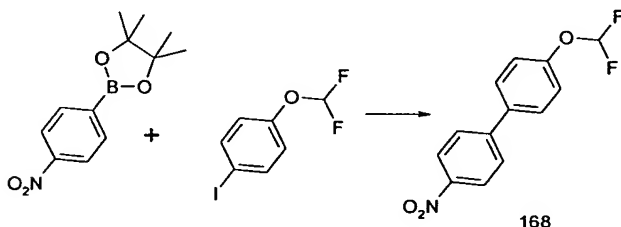


A suspension of 4-([4-(5-methoxy-pyridin-2-yl)-phenylamino]-
methyl)-5-methyl-furan-2-carboxylic acid hydrochloride salt
20 (**166**) (30mg, 0.08mmoles) in tetrahydrofuran (5ml) was
treated with toluene-2-sulphonamide (41mg, 0.24mmoles), 1-
(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
(34mg, 0.176mmoles) and 4-(*N,N*-dimethylamino)-pyridine
(10mg, 0.08mmoles) and the mixture stirred at room
25 temperature for 16 hours. Triethylamine (24.3mg, 0.24mmoles)

was added and the mixture was stirred for a further 18 hours. The reaction mixture was concentrated and the residue was purified by HPLC to afford compound **167** as a yellow glass (1.1mg). LC/MS System A; $R_t = 2.72$ mins, m/z (ES^+) = 492 ($M+H$ for $C_{26}H_{25}N_3O_5S$) and m/z (ES^-) = 490 ($M-H$ for $C_{26}H_{25}N_3O_5S$).

Example 40: Synthesis of 4-[(4'-Difluoromethoxy-biphenyl-4-ylamino)-methyl]-5-methyl-furan-2-carboxylic acid (171), N-{4-[(4'-Difluoromethoxy-biphenyl-4-ylamino)-methyl]-5-methyl-furan-2-carbonyl}-benzenesulfonamide (172), N-{4-[(4'-Difluoromethoxy-biphenyl-4-ylamino)-methyl]-5-methyl-furan-2-carbonyl}-2-methyl-benzenesulfonamide (173) and 3,5-Dimethyl-isoxazole-4-sulfonic acid {4-[(4'-difluoromethoxy-biphenyl-4-ylamino)-methyl]-5-methyl-furan-2-carbonyl}-amide (174)

(a) 4-Difluoromethoxy-4-nitro-biphenyl (**168**)

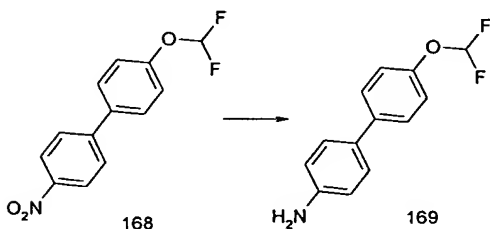


[1,1'-Bis(diphenylphosphino) ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (250mg) was added to a degassed mixture of 4,4,5,5-tetramethyl-2-(4-nitro-phenyl)-[1,3,2]dioxaborolane (1.67g, 6.70mmoles), 1-difluoromethoxy-4-iodo-benzene (2.17g, 8.04mmoles) and 2M aqueous cesium carbonate (10.05ml) in 1,4-dioxan (120ml). The mixture was placed under an argon atmosphere and was heated at 80°C for 20 hours. After cooling, the mixture was concentrated and the residue was partitioned between dichloromethane (2 x 200ml) and water (100ml). The combined extracts were washed with brine (150ml) and dried ($MgSO_4$). After evaporation of

the solvent, the residue was purified by flash chromatography, using petrol (60-80°)/diethyl ether 19:1v/v as eluent, to afford compound **168** (1.15g) as a beige coloured solid.

5

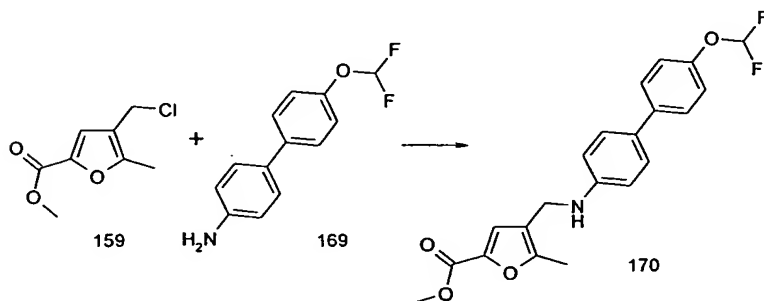
(b) 4'-Difluoromethoxy-biphenyl-4-ylamine (**169**)



A solution of 4-difluoromethoxy-4-nitro-biphenyl (**168**) (1.1g, 4.15mmoles) in ethyl acetate (100ml) was hydrogenated over 10% palladium on charcoal catalyst (250mg) using a hydrogen filled balloon. After 20 hours, the mixture was filtered through a pad of diatomaceous earth and the pad rinsed with ethyl acetate. The combined filtrate and washings were evaporated to afford compound **169** (855mg) as a solid. LC/MS System A; $R_t = 2.87$ mins, m/z (ES^+) = 236 ($M+H$) and 277 ($M+H$ acetonitrile adduct) for $C_{13}H_{11}F_2NO$.

10

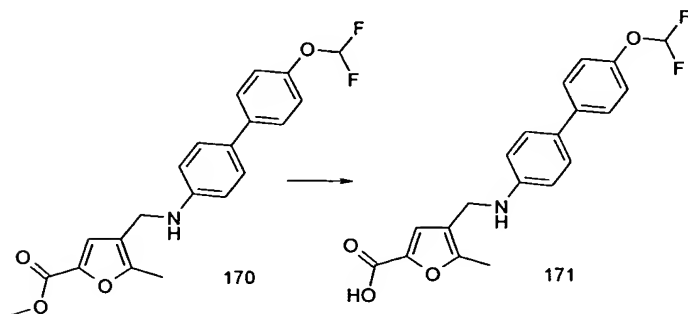
(c) 4-(4'-Difluoromethoxy-biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**170**)



20

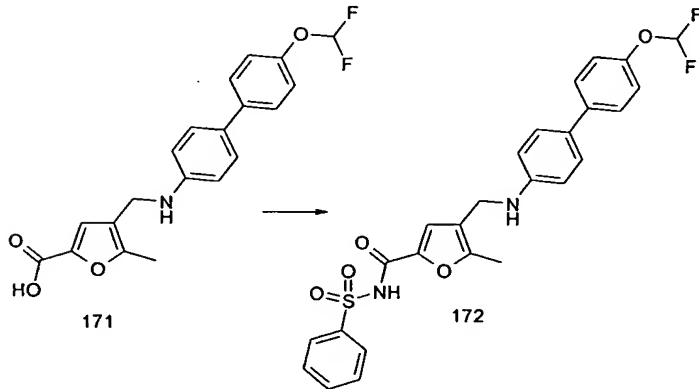
Compound (**170**) was prepared from compounds (**159**) and (**169**) by adapting the procedure of Example 38(d). (420mg). LC/MS System A; $R_t = 4.00$ mins, m/z (ES^+) = 388 ($M+H$) and 429 ($M+H$ acetonitrile adduct) for $C_{21}H_{19}F_2NO_3$.

(d) 4-(4'-Difluoromethoxy-biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carboxylic acid (**171**)



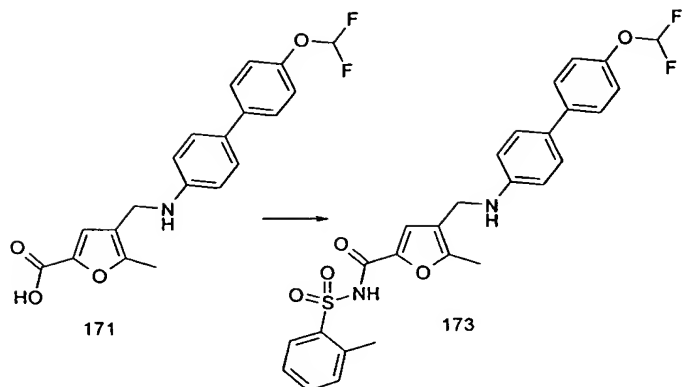
5 Compound (**171**) was prepared from compound (**170**) by adapting the procedure of Example 38(e). LC/MS System D; R_t = 9.07mins, m/z (ES^+) = 374 ($M+H$ for $C_{20}H_{17}F_2NO_4$).

10 (e) N-{4-[(4'-Difluoromethoxy-biphenyl-4-ylamino)-methyl]-5-methyl-furan-2-carbonyl}-benzenesulphonamide (**172**)



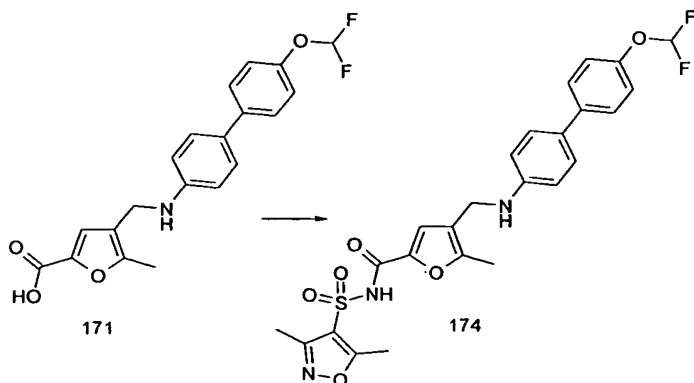
15 Compound (**172**) was prepared from compound (**171**) and benzenesulphonamide by adapting the procedure of Example 38(f). LC/MS System D; R_t = 10.38mins, m/z (ES^+) = 513 ($M+H$ for $C_{26}H_{22}F_2N_2O_5S$).

(f) N-{4-[(4'-Difluoromethoxy-biphenyl-4-ylamino)-methyl]-5-methyl-furan-2-carbonyl}-2-methyl-benzenesulphonamide (**173**)



Compound (173) was prepared from compound (171) and 2-methyl-benzenesulphonamide by adapting the procedure of Example 38(f). LC/MS System D; $R_t = 10.63\text{mins}$, m/z (ES^+) = 527 ($\text{M}+\text{H}$ for $\text{C}_{27}\text{H}_{24}\text{F}_2\text{N}_2\text{O}_5\text{S}$).

(d) 3,5-Dimethyl-isoxazole-4-sulphonic acid {4-[(4'-difluoromethoxy-biphenyl-4-ylamino)-methyl]-5-methyl-furan-2-carbonyl}-amide (174)

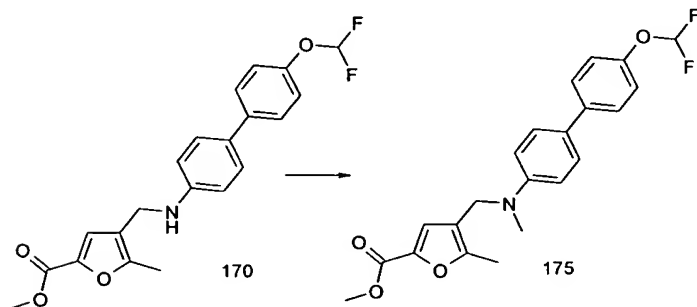


Diisopropylethylamine (60 μl , 0.339mmoles) and a solution of 4-(4'-difluoromethoxy-biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carboxylic acid (171) (50mg, 0.103mmoles) in N,N-dimethylformamide (1.0ml) were added to a stirred solution of 3,5-dimethyl-isoxazole-4-sulphonic acid amide (55mg, 0.308mmoles) in N,N-dimethylformamide (5.0ml). A solution of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (46mg, 0.124mmoles) in N,N-dimethylformamide (1.0ml) was added and the mixture was

stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by HPLC to afford compound **174** (2mg) as a solid. LC/MS System D; $R_t = 10.35$ mins, m/z (ES^+) = 532 ($M+H$ for $C_{25}H_{23}F_2N_3O_6S$).

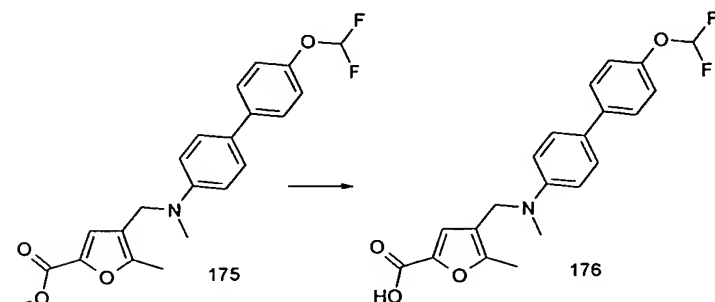
Example 41: Synthesis of 4-[[[(4'-Difluoromethoxy-biphenyl-4-yl)-methyl-amino]-methyl]-5-methyl-furan-2-carboxylic acid (176) and N-(4-[[[(4'-Difluoromethoxy-biphenyl-4-yl)-methyl-amino]-methyl]-5-methyl-furan-2-carbonyl)-2-methyl-benzenesulfonamide (177)

(a) 4-[[[(4'-Difluoromethoxy-biphenyl-4-yl)-methyl-amino]-methyl]-5-methyl-furan-2-carboxylic acid methyl ester (**175**)



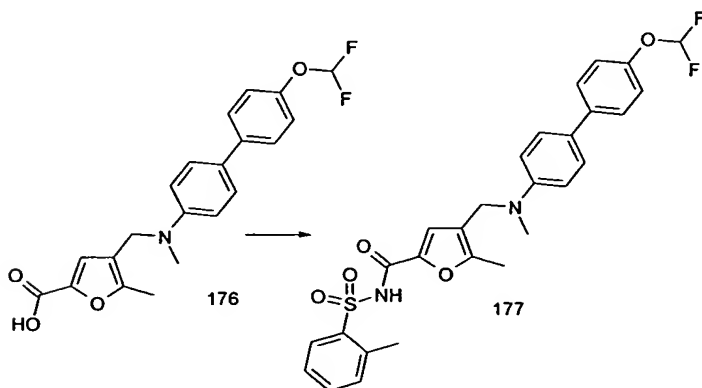
Iodomethane (91mg, 0.64mmoles) and potassium carbonate (88mg, 0.64mmoles) were added to a solution of 4-(4'-difluoromethoxy-biphenyl-4-ylaminomethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**170**) (62mg, 0.16mmoles) in *N,N*-dimethylformamide (10ml) and the mixture stirred at room temperature for 36 hours under an argon atmosphere. The mixture was then heated at 35°C for 21 hours. The mixture was partitioned between dichloromethane and water, the organic phase separated and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by flash chromatography, using cyclohexane/ethyl acetate 99:1v/v as eluent, to afford compound **175** (41mg) as a brown oil. This was used directly in part (b).

(b) 4-[[(4'-difluoromethoxy-biphenyl-4-yl)-methyl-amino]-methyl]-5-methyl-furan-2-carboxylic acid (**176**)



A solution of 4-[[(4'-difluoromethoxy-biphenyl-4-yl)-methyl-amino]-methyl]-5-methyl-furan-2-carboxylic acid methyl ester (**175**) (30mg, 0.07mmoles) in dry tetrahydrofuran (20ml) was treated with potassium trimethylsilanoate (19mg, 0.15mmoles) and the mixture stirred under an argon atmosphere for 30 hours. Trifluoroacetic acid was added until the pH = 2.
After evaporation of the solvent, the residue was purified by HPLC to afford compound **176** (4.8mg) as a white solid. LC/MS System D; R_t = 9.42mins, m/z (ES^+) = 388 ($M+H$ for $C_{21}H_{19}F_2NO_4$).

(c) N-(4-[[(4'-difluoromethoxy-biphenyl-4-yl)-methyl-amino]-methyl]-5-methyl-furan-2-carbonyl)-2-methyl-benzenesulfonamide (**177**)



A stirred solution of 4-[[(4'-difluoromethoxy-biphenyl-4-yl)-methyl-amino]-methyl]-5-methyl-furan-2-carboxylic acid (**176**) (21mg, 0.054mmoles), 2-methyl-benzenesulphonamide

(19mg, 0.108mmoles) and 4-(N,N-dimethylamino)-pyridine (1mg) in a mixture of dichloromethane (8ml) and acetonitrile (2ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.4mg, 0.060mmoles). The mixture was stirred at room temperature for 18 hours under an argon atmosphere. The reaction mixture was concentrated *in vacuo* and the residue was purified by HPLC to afford compound **177** (2.9mg) as a solid. LC/MS System D; R_t = 11.21mins, m/z (ES^+) = 541 ($M+H$ for $C_{28}H_{26}F_2N_2O_5S$).

Example 42: Biological Results

Binding ability to human EP receptors

Membranes were prepared from cells stably transfected with human EP receptor cDNA. In brief, cells were cultured to confluency, scraped from culture flasks, and centrifuged (800 g, 8 minutes, 4°C). Cells were twice washed in ice cold homogenisation buffer containing 10 mM Tris-HCl, 1 mM EDTA.2Na, 250 mM sucrose, 1 mM PMSF, 0.3 mM indomethacin, pH 7.4, homogenised and re-centrifuged as before. The supernatant was stored on ice and pellets re-homogenised and re-spun. Supernatants were pooled and centrifuged at 40000g, 10 minutes, 4°C. Resultant membrane pellets were stored at -80°C until use.

For assay, membranes expressing human EP₄, EP₃, EP₂ or EP₁ receptors were incubated in Millipore (MHVBN45) plates containing assay buffer, radiolabelled [³H]PGE₂ and 0.1 to 10 000 nM concentrations of compounds. Incubations were performed at suitable temperatures and for suitable times to allow equilibrium to be reached. Non-specific binding was determined in the presence of 10uM PGE₂. Bound and free radiolabel was separated by vacuum manifold filtration using appropriate wash buffers, and bound radiolabel was

determined by scintillation counting. Constituents of each of the buffers are included in table 1 below.

The affinity or pK_i of each compound for each receptor was calculated from the concentration causing 50% radioligand displacement (IC_{50}) using the Cheng-Prusoff equation:

$$K_i = \frac{IC_{50}}{1 + \left(\frac{\text{radioligand concentration}}{\text{radioligand } KD} \right)}$$

This approach follows that set out in Kenakin, T.P., Pharmacologic analysis of drug receptor interaction. Raven Press, New York, 2nd edition.

Table 1

Receptor		EP ₁	EP ₂	EP ₃	EP ₄
Protein / well		6.5µg	8µg	5µg	5µg
Final [³ H-PGE ₂]		3.6nM	3nM	2.5nM	1nM
Buffer	Assay	10mM MES pH6.0; 10mM MgCl ₂ ; 1mM EDTA, 3uM Indomethacin	10mM MES pH6.0; 10mM MgCl ₂ ; 1mM EDTA	10mM MES pH 6.0; 10mM MgCl ₂ ; 1mM EDTA, 100uM GTP-gamma-S	10mM MES pH6.0; 10mM MgCl ₂ ; 1mM EDTA, 3uM Indomethacin
	Wash	10mM MES pH6.0; 10mM MgCl ₂	10mM MES pH6.0; 10mM MgCl ₂	10mM MES pH 6.0; 10mM MgCl ₂	10mM MES pH6.0; 1mM EDTA

The results are presented as pK_i values in table 2 below.

Table 2

Compound	EP ₄	EP ₁	EP ₂	EP ₃
4	>6.5	-	<5	<5
5	>7.5	-	<5.5	<5
6	>8	-	<5	<5
7	>6.5	-	<5	<5
8	>8	-	<5	<5
9	>8	-	<5	<5
10	>8	-	<5.5	<5
11	>7.5	-	<5	<5
12	>7	-	<5	<5
13	>8	-	<5	<5
19	>6.5	-	<5	<5
21	>6.5	-	<5	<5
22	>8	-	<5	<5
24	>6.5	<5	<5	<5
25	>6.5	-	<5	<5
27	>6	-	<5.5	<5
28	>6	-	<5	<5
37	>6.5	-	<5	<5
38	>6	-	<5.5	<5
39	>7	-	<5	<5
40	>7	-	<5	<5
42	>7	-	<5	<5
43	>7	-	<5	<5
46	>7	-	<5	<5
49	>8	<5	<5	<5
50	>5.5	-	<5.5	<5
53	>5.5	-	<5	<5
56	>5.5	-	<4.5	<5
57	>5	-	<5	<5
59	>5.5	-	<5	<5

60	>8	<5	<5	<5
61	>6	-	<5	<5
62	>7	-	<5	<5
63	>6.5	-	<5	<5
64	>7	-	<5	<5
67	>6	-	<5	<5
68	>6	-	<5	<5
69	>7	-	-	-
72	>5	-	<5	<5
73	>5.5	-	<5	<5
74	>5.5	-	<5	<5
77	>5.5	-	<5	<5
78	>5	-	<5.5	<5
79	>5.5	-	<5	<5
80	>6.5	-	<5	<5
81	>5.5	-	<5.5	<5
85	>5.5	-	<5	<5
86	>6	-	<5	<5
87	>5.5	-	<5	<5
90	>5.5	-	<5	<5
91	>5.5	-	<5	<5
92	>5.5	-	<5	<5
93	>5.5	-	<5	<5
94	>6.5	-	<5	<5
95	>5.5	-	<5.5	<5
96	>5.5	-	<5	<5
98	>6.5	-	<5	<5
99	>6	-	<5.5	<5
100	>5.5	-	<5	<5
102	>5.5	-	<5.5	<5
104	>6	-	<5.5	<5
105	>5.5	-	<5	<5
108	>5.5	-	<5	<5

109	>5.5	-	<5	<5
110	>5.5	-	<5	<5
111	>5.5	-	<5	<5
112	>5.5	-	<5	<5
113	>5	-	<5	<5
114	>5.5	-	<5	<5
115	>5	-	<5	<5
116	>6	-	<5	<5
117	>5.5	-	<5	<5
118	>6	-	<5	<5
122	>7	-	<5	<5
126	>5.5	-	<5	<5
127	>7	-	<5	<5
129	>7.5	-	<5	<5
130	>8	-	<5.5	<5
131	>8.5	-	<5.5	<5
132	>7.5	-	<5	<5
133	>7.5	-	<5	<5
134	>7.5	-	<5	<5
135	>5	-	<5	<5
137	>5	-	<5	<5
138	>5.5	-	<5	<5
140	>5.5	-	<5	<5
141	>6.5	-	<5	<5
142	>7	-	<5	<5
144	>6	-	<5	<5
145	>7.5	-	<5	<5
146	>7.5	-	<5	<5
149	>7	-	<5	<5
153	>6	-	<5	<5
154	>7.5	-	<5.5	<6
155	>6	-	<5.5	<5.5
156	>5	-	<5	<5

156a	>5	-	<5	<5
160	>5.5	-	<5	<5
161	>7.5	-	<5	<5
162	>8.0	-	<5	<5
167	>6.5	-	<5	<5
171	>6.5	-	<5	<5
172	>8	-	<5	<5
173	>8	-	<5.5	<5
174	>8	-	<5	<5
176	>6.5	-	<5	<5
177	>7.5	-	<5	<5